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Novel alcohol dehydrogenases

The invention relates to novel polypeptides which have the biological activity of an NAD- or NADP-dependent alcohol dehydrogenase. The invention furthermore relates to nucleic acids encoding said polypeptides, to nonhuman hosts or host cells and to reaction systems which may be used for preparing desired products. The polypeptides of the invention are preferably used in the preparation, starting from aldehydes or ketones, of primary and enantiomerically pure secondary alcohols which may serve as intermediates for medicaments. Alternatively, the polypeptides of the invention may also be employed in the reverse reaction, i.e. the oxidation of alcohols with the formation of aldehydes or ketones.

The description makes reference to a number of documents. The disclosure content of these documents is hereby incorporated by reference.

Enantiomerically pure alcohols are among the most important chiral building blocks of industrial special and fine chemistry. These products act, inter alia, as essential key intermediates in the preparation of medicaments. For a long time, the industrial route to these target molecules went preferably via purely chemical processes, for example by way of resolution of the racemate. This involves, starting from a ketone, firstly preparing the alcohol in its racemic form and then isolating the desired enantiomer in a resolution of the racemate with the aid of at least stoichiometric amounts of a chiral auxiliary substance. Disadvantages of these methods include not only the 50% maximum yield of the resolution of the racemate but must also be seen in the use of numerous ecologically problematic starting compounds for preparing the racemate. Further disadvantages are the additional step of recycling the undesired enantiomer as well as the need of chiral auxiliary reagents (moreover, stoichiometric amounts

thereof) for the resolution of the racemate. The concept of the resolution of the racemate is summarized in the equation (1a) in the overview in Figure 1. A first substantial progress toward a more sustainable process was achieved using the biocatalytic resolution of the racemate, thereby dispensing with the necessity of employing stoichiometric amounts of chiral auxiliary reagents. Regrettably, however, all other disadvantages listed above remained relevant, despite such a biocatalytic route.

One possible way of avoiding the above-described disadvantages of the resolution of the racemate or of diastereoselective syntheses is the direct conversion of ketones to the desired optically active alcohols in one step. Such "direct asymmetrical processes" may be carried out firstly by using metal-containing chemocatalysts, with the chemocatalysts employed being heavy metal-containing complexes which include a chiral ligand. Besides the use of ecologically problematic heavy metals as a substantial catalyst component, the need for expensive and partly very sensitive ligands, for example phosphane ligands, is also disadvantageous.

Another alternative is the direct asymmetrical reduction using suitable biocatalysts for quantitative conversion of prochiral substrates to the desired enantiomerically pure product. Here too, the number of reaction steps is reduced to the theoretically possible minimum of only one step, the biocatalytic conversion is carried out under ecologically excellent conditions (inter alia water as a solvent), and the process as such proceeds with high atom economy. The concept of a biocatalytic and sustainable process of this kind is set out in the equation (1b) of the overview in Figure 1.

One disadvantage of the biocatalytic variant, however, is the lack of alcohol dehydrogenases available on an

industrial scale as suitable biocatalysts for the target reaction and expression thereof. The object on which the present invention is based was therefore to obtain novel, efficient and industrially usable alcohol dehydrogenases. This object is achieved by the embodiments characterized in the claims.

Thus, the invention relates to a polypeptide which has the biological activity of an NAD- or NADP-dependent alcohol dehydrogenase and which comprises or has one of the following sequences: the sequence of SEQ ID NO.: 1, the sequence of SEQ ID NO.: 2, the sequence of SEQ ID NO.: 3 or a sequence which is at least 90% identical to the sequence of SEQ ID NO.: 3. Said sequence is preferably at least 95% identical to SEQ ID NO.: 3. More preferably, said sequence is at least 98% or 99% identical to SEQ ID NO.: 3. Also comprised is the sequence of SEQ ID NO.: 4. Furthermore comprised is the sequence of SEQ ID NO.: 5 or a sequence which is at least 90% identical to the sequence of SEQ ID NO.: 5. Preferably, said sequence is at least 95% identical to SEQ ID NO.: 5. More preferably, said sequence is at least 98% or 99% identical to SEQ ID NO.:5. Also comprised is the sequence of SEQ ID NO.: 6 or a sequence which is at least 90% identical to the sequence of SEQ ID NO.: 6. Preferably, said sequence is at least 95% identical to SEQ ID NO.: 6. More preferably, said sequence is at least 98% or 99% identical to SEQ ID NO.: 6. Likewise comprised is the sequence of SEQ ID NO.: 7 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 7. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 7. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 7. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 7. Also comprised is the sequence of SEQ ID NO.: 8 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 8. Preferably, said sequence is at least 75% identical

to SEQ ID NO.: 8. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 8. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 8.

Additionally comprised is the sequence of SEQ ID NO.: 9 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 9. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 9. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 9. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 9. Likewise comprised is the sequence of SEQ ID NO.: 10 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 10. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 10. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 10. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 10. Also comprised is the sequence of SEQ ID NO.: 11 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 11. Preferably, said sequence is at least 75% identical to sequence SEQ ID NO.: 11. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 11. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 11. Furthermore comprised is the sequence of SEQ ID NO.: 12 or a sequence which is at least 60% identical to the sequence of SEQ ID NO.: 12. Preferably, said sequence is at least 65% identical to SEQ ID NO.: 12. More preferably, said sequence is at least 70% identical to the sequence of SEQ ID NO.: 12. Even more preferably, said sequence is at least 75% or 80% identical to SEQ ID NO.: 12. Particularly preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 12. Likewise comprised is the sequence of SEQ ID NO.: 13 or a sequence which is at least

60% identical to the sequence of SEQ ID NO.: 13. Preferably, said sequence is at least 65% identical to SEQ ID NO.: 13. More preferably, said sequence is at least 70% identical to the sequence of SEQ ID NO.: 13. Even more preferably, said sequence is at least 75% or 80% identical to SEQ ID NO.: 13. Particularly preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 13. Also comprised is the sequence of SEQ ID NO.: 14 or a sequence which is at least 75% identical to the sequence of SEQ ID NO.: 14. Preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 14. More preferably, said sequence is at least 85% identical to the sequence of SEQ ID NO.: 14. Even more preferably, said sequence is at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 14. Additionally comprised is the sequence of SEQ ID NO.: 15 or a sequence which is at least 95% identical to the sequence of SEQ ID NO.: 15. Preferably, said sequence is at least 98% or 99% identical to the sequence of SEQ ID NO.: 15. Also comprised is the sequence of SEQ ID NO.: 16 or a sequence which is at least 95% identical to the sequence of SEQ ID NO.: 16. Preferably, said sequence is at least 98% or 99% identical to the sequence of SEQ ID NO.: 16. Furthermore comprised is the sequence of SEQ ID NO.: 17 or a sequence which is at least 75% identical to the sequence of SEQ ID NO.: 17. Preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 17. More preferably, said sequence is at least 85% identical to the sequence of SEQ ID NO.: 17. Even more preferably, said sequence is at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 17. Likewise comprised is the sequence of SEQ ID NO.: 18 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 18. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 18. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 18. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ

ID NO.: 18. Also comprised is the sequence of SEQ ID NO.: 19 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 19. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 19. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 19. Even more preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 19. Additionally comprised is the sequence of SEQ ID NO.: 20 or a sequence which is at least 60% identical to the sequence of SEQ ID NO.: 20. Preferably, said sequence is at least 65% identical to SEQ ID NO.: 20. More preferably, said sequence is at least 70% identical to the sequence of SEQ ID NO.: 20. Even more preferably, said sequence is at least 75% or 80% identical to SEQ ID NO.: 20. Particularly preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 20. Also comprised is the sequence of SEQ ID NO.: 21 or a sequence which is at least 90% identical to the sequence of SEQ ID NO.: 21. Preferably, said sequence is at least 95% identical to the sequence of SEQ ID NO.: 21. More preferably, said sequence is at least 98% or 99% identical to the sequence of SEQ ID NO.: 21. Furthermore comprised is the sequence of SEQ ID NO.: 22 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 22. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 22. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 22. Particularly preferably said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 22. Likewise comprised is the sequence of SEQ ID NO.: 23 or a sequence which is at least 55% identical to the sequence of SEQ ID NO.: 23. Preferably, said sequence is at least 60% identical to SEQ ID NO.: 23. More preferably, said sequence is at least 65% identical to the sequence of SEQ ID NO.: 23. Even more preferably, said sequence is at least 70% or 75% identical to SEQ ID NO.: 23. Particularly preferably, said sequence is at least 80%, 85%, 90%, 95%, 98% or 99%

identical to the sequence of SEQ ID NO.: 23. Also comprised is the sequence of SEQ ID NO.: 24 or a sequence which is at least 65% identical to the sequence of SEQ ID NO.: 24. Preferably, said sequence is at least 70% identical to SEQ ID NO.: 24. More preferably, said sequence is at least 75% identical to the sequence of SEQ ID NO.: 24. Even more preferably, said sequence is at least 80% or 85% identical to SEQ ID NO.: 24. Particularly preferably, said sequence is at least 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 24. Furthermore comprised is the sequence of SEQ ID NO.: 25 or a sequence which is at least 55% identical to the sequence of SEQ ID NO.: 25. Preferably, said sequence is at least 60% identical to SEQ ID NO.: 25. More preferably, said sequence is at least 65% identical to the sequence of SEQ ID NO.: 25. Even more preferably, said sequence is at least 70% or 75% identical to SEQ ID NO.: 25. Particularly preferably, said sequence is at least 80%, 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 25. Also comprised is the sequence of SEQ ID NO.: 26 or a sequence which is at least 55% identical to the sequence of SEQ ID NO.: 26. Preferably, said sequence is at least 60% identical to SEQ ID NO.: 26. More preferably, said sequence is at least 65% identical to the sequence of SEQ ID NO.: 26. Even more preferably, said sequence is at least 70% or 75% identical to SEQ ID NO.: 26. Particularly preferably, said sequence is at least 80%, 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 26. Likewise comprised is the sequence of SEQ ID NO.: 27 or a sequence which is at least 55% identical to the sequence of SEQ ID NO.: 27. Preferably, said sequence is at least 60% identical to SEQ ID NO.: 27. More preferably, said sequence is at least 65% identical to the sequence of SEQ ID NO.: 27. Even more preferably, said sequence is at least 70% or 75% identical to SEQ ID NO.: 27. Particularly preferably, said sequence is at least 80%, 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 27. Furthermore comprised is the sequence of SEQ ID NO.: 28 or a sequence

which is at least 75% identical to the sequence of SEQ ID NO.: 28. Preferably, said sequence is at least 80% identical to SEQ ID NO.: 28. More preferably, said sequence is at least 85% identical to the sequence of SEQ ID NO.: 28. Even more preferably, said sequence is at least 90%, 95%, 98% or 99% identical to SEQ ID NO.: 28. Likewise comprised is the sequence of SEQ ID NO.: 29 or a sequence which is at least 70% identical to the sequence of SEQ ID NO.: 29. Preferably, said sequence is at least 75% identical to SEQ ID NO.: 29. More preferably, said sequence is at least 80% identical to the sequence of SEQ ID NO.: 29. Even more preferably, said sequence is at least 85% or 90% identical to SEQ ID NO.: 29. Particularly preferably, said sequence is at least 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 29. Also comprised is the sequence of SEQ ID NO.: 30 or a sequence which is at least 60% identical to the sequence of SEQ ID NO.: 30. Preferably, said sequence is at least 65% identical to SEQ ID NO.: 30. More preferably, said sequence is at least 70% identical to the sequence of SEQ ID NO.: 30. Even more preferably, said sequence is at least 75% or 80% identical to SEQ ID NO.: 30. Particularly preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 30. Furthermore comprised is the sequence of SEQ ID NO.: 31 or a sequence which is at least 55% identical to the sequence of SEQ ID NO.: 31. Preferably, said sequence is at least 60% identical to SEQ ID NO.: 31. More preferably, said sequence is at least 65% or 70% identical to the sequence of SEQ ID NO.: 31. Even more preferably, said sequence is at least 75% or 80% identical to SEQ ID NO.: 31. Particularly preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 31. Likewise comprised is the sequence of SEQ ID NO.: 32 or a sequence which is at least 55% identical to the sequence of SEQ ID NO.: 32. Preferably, said sequence is at least 60% identical to SEQ ID NO.: 32. More preferably, said sequence is at least 65% or 70% identical

to the sequence of SEQ ID NO.: 32. Even more preferably, said sequence is at least 75% or 80% identical to SEQ ID NO.: 32. Particularly preferably, said sequence is at least 85%, 90%, 95%, 98% or 99% identical to the sequence of SEQ ID NO.: 32. Furthermore comprised is the sequence of SEQ ID NO.: 33 or the sequence of SEQ ID NO.: 34. The amino acid sequences mentioned and characterized by SEQ IDs are preferably encoded by the DNA sequences referred to as SEQ ID numbers 35 to 68. Preference is further given to polypeptides which correspond to the naturally occurring enzymes over their full length. In another preferred embodiment, the polypeptides of the invention additionally comprise at least one heterologous amino acid section which characterizes said polypeptides as fusion proteins. Possible examples of heterologous components of the fusion protein of the invention are Tags (e.g. His-Tag or Flag-Tag) which may be used for purification of the fusion proteins of the invention. In other embodiments, the heterologous components may have their own enzymic activity. In such a case, the two enzymic components are preferably linked by a linker such as a flexible glycine or glycine-serine linker of 6-10 amino acids in length, in order to ensure the functionality of said components. The term "heterologous", as used herein, may mean, firstly, that the components of the fusion protein do not naturally occur covalently linked together and, secondly, that the components originate from different species. Fusion proteins are usually prepared using recombinant DNA technology (see Sambrook et al., loc. cit.).

According to the invention, the term "polypeptide which has the biological activity of an NAD- or NADP-dependent alcohol dehydrogenase" refers to a group of enzymes which catalyze the conversion of alcohols to aldehydes or ketones or the corresponding reverse reaction, i.e. the conversion of aldehydes to primary alcohols or ketones to secondary alcohols. The first-mentioned reaction corresponds in this

connection to an oxidative process, with the secondly mentioned type of reaction being a reductive process. The EC number of alcohol dehydrogenases (ADHs) is EC 1.1.1.1. The scope of protection of the invention comprises, in addition to the naturally occurring enzymes isolated in the course of the present invention, also those polypeptides which have the aforementioned identity values at the amino acid level compared to the polypeptides isolated from natural sources and which may likewise originate from natural sources. On the other hand, they may be modified by recombinant DNA technology in such a way that the enzymic activity is retained or essentially retained, as will be anticipated by the skilled worker (cf., for example, Sambrook et al, "Molecular Cloning, A Laboratory Handbook", 2nd edition 1989, CSH Press, Cold Spring Harbor, Ausubel et al. "Current Protocols in Molecular Biology", John Wiley & Sons, NY 2001). Thus, it is possible for amino acids which are not located at the active site and whose replacement with an amino acid "of the same kind" is not expected at first sight to result in a substantially altered three-dimensional structure to be replaced with an amino acid "of the same kind". For example, particular amino acids with nonpolar side chains (amino acids of the same kind), may be expected to be able to be substituted, for example valine for alanine, without this having a (substantial) influence on the biological function of the enzyme, on the enzymic activity in accordance with the invention. On the basis of his specialist knowledge, the skilled worker may draw corresponding conclusions also for the substitution of other types of amino acids (for example the replacement of basic amino acids with other basic amino acids or of amino acids with uncharged polar side chains with other amino acids from this group).

The percentage of identity to the amino acid sequences of the polypeptides isolated from natural sources, which are described in this description by SEQ ID numbers, may be

readily determined by the skilled worker using processes known in the prior art. A suitable program which may be used according to the invention is BLASTP (Altschul *et al*.. 1997. Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucleic Acids Res. 25(17):3389-3402.).

The invention also relates to a nucleic acid molecule which encodes the polypeptide of the invention.

The nucleic acid molecule of the invention may be a DNA molecule or an RNA molecule. Preference is given to the nucleic acid molecule being a cDNA molecule or an mRNA molecule. According to the invention, said DNA molecule may furthermore be a genomic DNA molecule. The invention also comprises embodiments in which said DNA molecule is a PNA molecule or another derivative of a DNA molecule. According to the invention, preference is given to DNA sequences comprising the DNA sequences according to SEQ ID numbers 35 to 68.

In order to achieve the object on which the invention is based, the following approach was pursued. Firstly, based on an extensive proprietary strain collection, prioritized strains were grown on plates and, after viability and purity controls had been carried out, also in liquid culture. The genomic DNA of these organisms was isolated from the harvested cell pellets. Based on the genomic DNA prepared, selected isolates were genetically screened for alcohol dehydrogenase genes via PCR typing by means of primers of the invention. In this context, even the amino acid sequence similarity due to homology of already known alcohol dehydrogenases did not readily allow oligonucleotide primers to be derived with the aid of which previously unidentified alcohol dehydrogenase genes may readily be amplified successfully. Initially, this approach was based on the hypothesis of particular sequence motifs

conserved in the previously known alcohol dehydrogenase genes also being present in the desired novel alcohol dehydrogenase genes. However, the sequence motifs conserved in the previously known alcohol dehydrogenase genes are unsuitable for deriving degenerated primers by processes known to the skilled worker (Kwok *et al*.. 1995. Design and use of mismatched and degenerate primers. In: PCR Primer , A laboratory Manual, Dieffenbach CW & Dveksler GS (Editors), Cold Spring Habor Laboratory Press, pp143-155; Compton T. 1990. Degenerate Primers for DNA Amplification. In: PCR Protocols, A Guide to Methods and Applications. Innis et al. (Editors) Academic Press, San Diego, pp39-34). The NAD- or NADP-dependent alcohol dehydrogenases are classified as long-chain, medium-chain and short-chain ADHs. They are divided into these three groups especially based on their metal dependence and the size of subunits. The short-chain ADHs do not require any metal ions and their subunits consist of approximately 250 amino acids. In contrast, the medium-chain and long-chain ADHs are dependent on metal ions. The medium-chain ones whose typical subunits consist of approx. 350 amino acids require zinc ions. The long-chain ADHs whose subunits are composed of approx. 385 amino acids require iron ions (Hummel, W. 1997. New alcohol dehydrogenases for the synthesis of chiral compounds. 58:145-84). The sequence heterogeneity, not only within all of the previously known NAD- or NADP-dependent ADHs but also within the three ADH groups briefly described above, is extremely high. Therefore, it was not that easy to construct primers with the aid of which it is possible firstly to amplify specifically ADH sequences and secondly also to capture a diversity of novel ADHs necessary in order to achieve the object. Thus, despite the sequence homologies expected on the basis of the used, no long-chain ADHs whatsoever were isolated in the bacteria studied. In this connection, it was intended to test the quality of the constructed primers first with genomic DNA of model organisms whose alcohol dehydrogenase genes are

known or with DNA pools consisting of DNA from various microorganisms. This involved cloning, sequencing and subsequently analyzing PCR products. After this establishing phase, selected isolates were subjected to PCR typing on the basis of the prepared genomic DNA of the microorganisms to be screened, as described above. The results obtained from the experiments (regarding sequence identity and specific activity) were incorporated into prioritizing the potential Hit organisms whose novel alcohol dehydrogenase genes are being isolated. Despite the unexpected, disappointing and demotivating results in the course of the attempted isolation of nucleic acids supposed to encode long-chain ADHs, a number of nucleic acids encoding short-chain enzymes and medium-chain enzyme chains were isolated according to the invention. Some of these enzymes and enzyme chains had surprisingly low sequence identities (<50%) to the known enzymes of this class.

The invention furthermore relates to a nucleic acid molecule which is complementary to the nucleic acid molecule of the invention.

According to the invention, the term "complementary" means a complementarity which extends across the entire region of the nucleic acid molecule of the invention without gaps. In other words, preference is given according to the invention to said complementarity extending 100% across the entire region of the sequence of the invention, i.e. from the 5′ end shown to the 3′ end shown. In further preferred embodiments, said complementarity extends across a region of at least 19, preferably at least 21, contiguous nucleotides which preferably do not code for the active site of enzymic activity.

In addition, the invention relates to a vector which comprises the nucleic acid molecule of the invention.

The vectors of the invention preferably contain the nucleic acids of the invention operatively linked to an expression control sequence so as for said nucleic acids to be able to be transcribed and, where appropriate, translated in a suitable host cell. Expression control sequences usually comprise a promoter and, where appropriate, further regulatory sequences such as operators or enhancers. Furthermore, translation initiation sequences may also be present. Suitable expression control sequences for prokaryotic or eukaryotic host cells are known to the skilled worker (see, for example, Sambrook et al., loc. cit.). The recombinant vector of the invention may furthermore also contain usual elements such as an origin of replication and a selection marker gene. Examples of suitable recombinant vectors are plasmids, cosmids, phages or viruses (see, for example, Sambrook et al., supra). Starting materials for preparing the recombinant vectors of the invention are commercially available (for example from Stratagene, InVitroGen or Promega).

Any plasmids or vectors available to the skilled worker for this purpose are suitable in principle. Plasmids and vectors of this kind may be found, for example, in Studier and coworkers (Studier, W. F.; Rosenberg A. H.; Dunn J. J.; Dubendroff J. W.; (1990), Use of the T7 RNA polymerase to direct expression of cloned genes, Methods Enzymol. 185, 61-89) or in the brochures from Novagen, Promega, New England Biolabs, Clontech or Gibco BRL. Further preferred plasmids and vectors may be found in: Glover, D. M. (1985), DNA cloning: a practical approach, Vol. I-III, IRL Press Ltd., Oxford; Rodriguez, R.L. and Denhardt, D. T (eds) (1988), Vectors: a survey of molecular cloning vectors and their uses, 179-204, Butterworth, Stoneham; Goeddel, D. V. (1990), Systems for heterologous gene expression, Methods Enzymol. 185, 3-7; Sambrook, J.; Fritsch, E. F. and Maniatis, T. (1989), Molecular cloning: a laboratory manual, 2nd ed., Cold Spring Harbor Laboratory Press, New

York. Plasmids which may be used for cloning the gene construct having the nucleic acid of the invention into the host organism in a very preferred manner are derivatives of: pUC18 and pUC19 (Roche Biochemicals), pKK-177-3H (Roche Biochemicals), pBTac2 (Roche Biochemicals), pKK223-3 (Amersham Pharmacia Biotech), pKK-233-3 (Stratagene) or pET (Novagen). Other preferred plasmids are pBR322 (DSM3879), pACYC184 (DSM4439) and pSC101 (DSM6202), which may be obtained from the DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Brunswick, Germany. Examples of preferred promoters are T7, lac, tac, trp, rha and ara.

The invention also relates to a nonhuman host which comprises the polypeptide of the invention or the nucleic acid molecule of the invention or the vector of the invention.

The nonhuman host may be a cell or a multi- to polycellular organism. Suitable polycellular organisms include model systems familiar in molecular biology, such as Drosophila melanogaster, zebra fish or C. elegans.
In a preferred embodiment, the host is a cell.

In this preferred embodiment, the host of the invention is a recombinant cell which has been transformed or transfected with a nucleic acid of the invention or a vector of the invention (according to the present invention, the terms "transformation" and "transfection" are used synonymously). Transformation or transfection may be carried out by known methods, for example calcium phosphate coprecipitation, lipofection, electroporation, particle bombardment or viral infection. The cell of the invention may contain the recombinant nucleic acid in an extrachromosomal or a chromosomally integrated form. In other words, the transfection/transformation may be stable or transient.

The recombinant cell preferably is of prokaryotic origin. Suitable host cells include cells of unicellular microorganisms, such as bacteria cells. A particularly suitable bacterial host system is E. coli. The cytoplasm of E. coli contains the cofactors required for the enzymic activity of the polypeptide of the invention. These are, in particular, NADH, NADPH, NAD^+ and $NADP^+$. Very particular preference is given to: E. coli XL1 Blue, W3110, DSM14459 (PCT/US00/08159), NM 522, JM101, JM109, JM105, RR1, DH5, TOP 10- or HB101. It is also possible to use for expression of the nucleic acids of the invention bacteria of the genera/species Lactobacillus, Bacillus, Rhodococus, Campylobacter, Caulobacter, Mycobacterium, Streptomyces, Neisseria, Ralstoni, Pseudomonas, and Agrobacterium. Appropriate strains are available in the prior art and may, at least partially, be obtained via the international deposition sites such as ATCC or DMSZ. Transfection protocols and transformation protocols are known to the skilled worker. (Chan and Cohen. 1979. High Frequency Transformation of Bacillus subtilis Protoplasts by Palsmid DNA. Mol Gen Genet. 168(1):111-5; Kieser *et al.*. 2000. Practical Streptomyces Genetics. The John Innes Foundation Norwich.; Sambrook *et al.*. 1989. Molecular Cloning. A Laboratory Manual. In: second ed.. Cold Spring Harbor Laboratory Press. Cold Spring Harbor. NY.; Irani and Rowe. 1997. Enhancement of transformation in *Pseudomonas aeruginosa* PAO1 by Mg^{2+} and heat. Biotechniques 22: 54-56). Additional examples of host organisms which may be used are also yeasts such as Hansenula polymorpha, Pichia sp., Saccharomyces cerevisiae. As an alternative to this, the cell may be of eukaryotic origin. Suitable eukaryotic cells include CHO cells, HeLa cells and others. Many of these cells are obtainable via deposition sites such as ATCC or DMSZ.

In a further preferred embodiment, the host is a transgenic nonhuman animal.

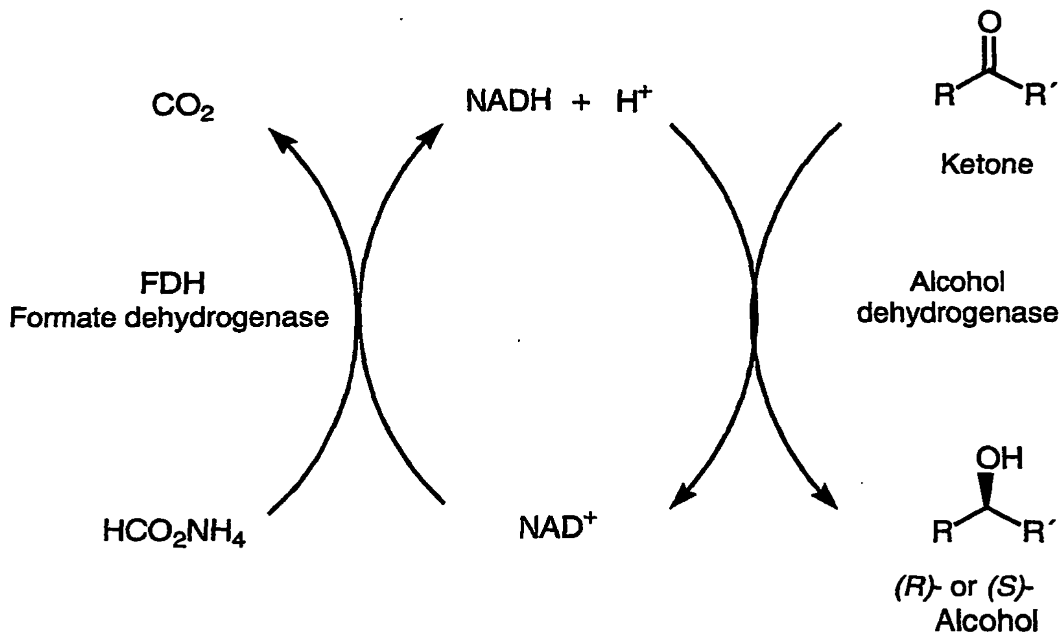
Transgenic nonhuman animals may be produced by processes known in the prior art.
The transgenic nonhuman animal of the invention may preferably have various genetic constitutions. It may (i) constitutively or inducibly overexpress the gene of a nucleic acid of the invention, (ii) contain the endogenous gene of a nucleic acid of the invention in an inactive form, (iii) contain the endogenous gene of a nucleic acid of the invention completely or partially replaced with a mutated gene of a nucleic acid of the invention, (iv) have conditional and tissue-specific overexpression or underexpression of the gene of a nucleic acid of the invention or (v) have a conditional and tissue-specific knock-out of the gene of a nucleic acid of the invention. Preferably, the transgenic animal additionally contains an exogenous gene of a nucleic acid of the invention under the control of a promoter allowing overexpression.
Alternatively, the endogenous gene of a nucleic acid of the invention may be overexpressed by activating or/and replacing the intrinsic promoter. Preferably, the endogenous promoter of the gene of a nucleic acid of the invention has a genetic modification which results in increased expression of the gene. Said genetic modification of the endogenous promoter here comprises both a mutation of individual bases and deletion and insertion mutations.

In a particularly preferred embodiment of the host of the invention, the latter is a transgenic rodent, preferably a transgenic mouse, a transgenic rabbit, a transgenic rat, or is a transgenic sheep, a transgenic cow, a transgenic goat or a transgenic pig.

Mice have numerous advantages over other animals. They can be kept easily and their physiology is regarded as a model system for that of humans. The production of such gene-manipulated animals is sufficiently known to the skilled

worker and carried out using common processes (see, for example, Hogan, B., Beddington, R., Costantini, F. and Lacy, E. (1994), Manipulating the Mouse-Embryo; A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; WO91/08216).
Alternatively or additionally, it is also possible to employ cell culture systems, in particular human cell culture systems, for the applications described for the nonhuman transgenic animal of the invention.
Examples of cofactors of alcohol dehydrogenases, which are used - as already mentioned, depending on the particular alcohol dehydrogenase - are NADH and NADPH and their oxidized forms, NAD^+ and $NADP^+$, respectively.

The cofactors may be regenerated, in principle, either in an enzyme-coupled manner using a second enzyme, for example a formate dehydrogenase or glucose dehydrogenase, or in a substrate-coupled manner using any of the alcohols accepted as substrate by the alcohol dehydrogenase employed, for example - *iso*-propanol - if accepted as substrate. The diagram below indicates by way of example the concept of the alcohol dehydrogenase-catalyzed reduction of a ketone with enzyme-coupled cofactor regeneration using a formate dehydrogenase.



Alcohol dehydrogenases are used, for example, for preparing enantiomerically enriched, preferably enantiomerically pure, secondary alcohols, starting from prochiral ketones. In this connection, both (R)- and (S)-specific alcohol dehydrogenases are known which accordingly result in the formation of the particular enantiomeric (R) and, respectively, (S) forms of alcohols.

Correspondingly, preference is also given according to the invention to a host which has a further dehydrogenase suitable for cofactor regeneration or a nucleic acid molecule encoding said dehydrogenase.

In this connection, the host may contain naturally said further dehydrogenase or may have been transfected with a recombinant nucleic acid which encodes said dehydrogenase and with which it is possible to express said dehydrogenase in said host. This embodiment also requires the host having the cofactors necessary for the function of said further dehydrogenase or said cofactors being delivered to said host in a suitable manner.

Particular preference is given in this connection to a host in which the dehydrogenase suitable for cofactor regeneration is a formate dehydrogenase or a glucose dehydrogenase. Particular preference is given to a *Candida boidinii* formate dehydrogenase. Particular preference is also given to the cofactor-regenerating dehydrogenase being a *Bacillus subtilis* glucose dehydrogenase. Genetically modified mutants of said cofactor-regenerating dehydrogenases, which retain said enzymic function, are likewise preferred according to the invention.

In a further embodiment, the invention relates to a reaction system which comprises an organic compound which is a substrate of a dehydrogenase, furthermore the polypeptide of the invention, the vector of the invention or the host of the invention and, where appropriate, a cofactor for the polypeptide of the invention. (The addition of cofactor is required in those cases in which the cofactor is not already present in the system, see also hereinbelow). In one case, the reaction system of the invention may be a bacterial cell which corresponds to the host of the invention and which has the polypeptide of the invention and also the necessary cofactors in the cytoplasm. In the case of the cofactor(s) already being present naturally in the system/host, said cofactors need no longer be delivered separately. Suitably, the host is one which has a further dehydrogenase suitable for cofactor regeneration or a nucleic acid molecule encoding said dehydrogenase and also the cofactors required therefor. If a substrate for a desired product is supplied to said reaction system or if said substrate is metabolized in the reaction system itself, then the desired product may readily be isolated from the reaction system, if said reaction system is maintained under suitable conditions. Suitable conditions include carrying out the reaction at temperatures of from 10 to 80°C, preferably from 20 to 60°C, and very preferably from 20 to 40°C. Preference is

also given to the substrate concentration being from 100 to 2000 mM, preferably from 200 to 800 mM. In a preferred form, the desired reaction is carried out so as to achieve conversions of >80%, in particular >90%, within a reaction time of <20 hours, in particular a reaction time of <10 hours and very preferably a reaction time of <5 hours. In another embodiment, the reaction system may be an in vitro system for converting a suitable substrate to obtain the desired product. For example, the polypeptide of the invention may be contacted with the cofactors mentioned and the substrate and, where appropriate (i.e. if necessary), with a further dehydrogenase suitable for cofactor regeneration (and, where appropriate, cofactors required therefor, in particular NADH and/or NADPH their oxidized forms) under suitable conditions, as set out above, for example, and over a sufficient period of time, so that the desired product may be generated. In this in vitro variant with utilization of isolated enzymes (in purified form or as crude extract) and addition of cofactors, these cofactor additions should, in accordance with an economical process control, be <0.01 equivalents (based on the amount of substrate employed), preferably <0.001 equivalents and very preferably <0.0005 equivalents.

The "reaction system" may moreover also be a transgenic nonhuman animal to which a suitable substrate and, where appropriate, cofactors or/and said further dehydrogenase is fed or administered and which is capable of converting said substrate in suitable tissues. In another embodiment, the reaction system may also be a cellular membrane system in which the enzyme, the enzymes and, where appropriate, the cofactors are anchored.

Further preference is given according to the invention to a reaction system in which the organic compound which is a substrate of a dehydrogenase is a carbonyl compound.

Particular preference is given to a reaction system in which the carbonyl compound is an aldehyde or a ketone.

This embodiment of the invention permits the preparation, particularly preferred according to the invention, of technical grade alcohols which may be used, for example, as intermediates for the preparation of active compounds usable in medicaments.

Particular preference is given according to the invention to the ketone being an asymmetrically substituted ketone.

This embodiment of the invention is particularly preferred because the products generated in a corresponding reduction have a center of chirality and may be obtained with high enantioselectivity. In general, the desired chiral secondary alcohols are obtained in an enantiomerically pure form with an enantiomeric excess of >99%.

In another preferred embodiment of the reaction system of the invention, the organic compound which is a substrate of a dehydrogenase is an alcohol. This variant is preferably suitable for preparing commercially important carbonyl compounds, for example ketones relevant in the field of aroma chemicals. In addition, oxidation may also be utilized for the formation of enantiomerically pure, secondary alcohols by starting from a racemic alcohol as substrate and converting the undesired enantiomer into the ketone compound by enantioselective oxidation. The remaining, desired enantiomer may then be isolated accordingly.

The alcohol is preferably a primary alcohol or a chiral secondary alcohol. In the first case, the product generated is an aldehyde, whereas in the second case the corresponding ketones are formed.

Preference is also given according to the invention to the cofactor in the reaction system of the invention being NADH, NADPH, NAD^+ or $NADP^+$.

The invention also relates to a process for preparing the polypeptide of the invention or a polypeptide encoded by the nucleic acid molecule of the invention, which process comprises growing the host of the invention and isolating said polypeptide.

The polypeptide may be purified, for example, by conventional processes, for example by disrupting appropriate cells, for example by means of a "French press", by ion exchange, size selection or affinity chromatography etc. (Coligan *et al*.. Current Protocols in Protein Science, John Wiley & Sons, Inc.). As an alternative to this, the polypeptide of the invention, when linked to a leader peptide, may be exported out of the cells and purified from the culture supernatant. This embodiment requires the polypeptide of the invention, which does not naturally contain a leader peptide, to be genetically modified. This embodiment has the advantage of a simpler purification of the polypeptide of the invention from the culture supernatant. The best procedures and suitable leader peptides may be readily determined by the skilled worker.

In a further preferred embodiment of the process of the invention, the polypeptide is isolated from a body fluid or tissue sample of the nonhuman transgenic animal. In this embodiment too, the polypeptide of the invention preferably contains a leader peptide.
In a further preferred embodiment of the process of the invention and, in particular, if the nonhuman transgenic animal is a mammal, for example a cow, a goat or a sheep, the body fluid is milk or serum.

In another embodiment, the invention relates to a process for preparing an organic compound which is a product of a dehydrogenase, which process comprises reacting an organic compound which is a substrate of a dehydrogenase with the polypeptide of the invention, the host of the invention or by means of the reaction system of the invention.

The various embodiments of the invention which are to be used in the process of the invention differ in principle in that further components such as cofactors etc. (cf. supra) have to be added to the polypeptide, if the latter is used in a cell-free in vitro system. When using the reaction system of the invention, the necessary components, with the possible exception of the substrate, are preferably and advantageously already present in the system, and a separate addition is thus not needed here.

Preference is given according to the invention to a process which further comprises the step of isolating the product of the reaction. Suitable processes for isolation/purification have been set forth above.

In a particularly preferred embodiment of the process of the invention, the latter further comprises processing the product to give a medicament. A number of descriptions of utilizing enantiomerically pure alcohols as intermediates for preparing pharmaceutical active compounds are given in the literature. An overview in this respect is contained, inter alia, in: A. Kleemann, J. Engels, B. Kutscher, D. Reichert, Pharmaceutical Substances: Syntheses, Patents, Applications, 4th edition, Thieme-Verlag, Stuttgart, 2001.

In another, particularly preferred embodiment of the process of the invention, the latter further comprises the step of processing the product to give a secondary product. In this connection, derivatization may take place both by way of modification of the alcohol group, for example by

esterification and subsequent secondary reactions, and by way of modifications of the particular substituents.

Particular preference is given here to the process of the invention further comprising the step of formulating the secondary product with a pharmaceutically compatible carrier or excipient or diluent in the preparation of a medicament.

Examples of suitable pharmaceutically compatible carriers and/or diluents are known to the skilled worker and comprise, for example, phosphate-buffered saline solutions, water, emulsions such as, for example, oil/water emulsions, various types of wetting agents or detergents, sterile solutions, etc. Medicaments comprising such carriers may be formulated by means of known conventional methods. Said medicaments may be administered in a suitable dose to an individual. The administration may be carried out orally or parenterally, for example intravenously, intraperitoneally, subcutaneously, intramuscularly, locally, intranasally, intrabronchially, orally or intradermally, or via a catheter at a site in an artery. Preparations for parenteral administration comprise sterile aqueous or nonaqueous solutions, suspensions and emulsions. Examples of nonaqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as, for example, olive oil, and organic ester compounds such as, for example, ethyl oleate, which are suitable for injections. Aqueous carriers comprise water, alcohol/water-based solutions, emulsions, suspensions, salt solutions and buffered media. Parenteral carriers comprise sodium chloride solutions, Ringer dextrose, dextrose and sodium chloride, Ringer lactate and bound oils. Examples of intravenous carriers include liquid, nutrient and electrolyte supplements (such as, for example, those based on Ringer dextrose). The medicament may moreover comprise preservants and other additives such as, for example, antimicrobial compounds, antioxidants,

complexing agents and inert gases. Depending on the intended specific usage, other active compounds such as, for example, interleukins, growth factors, differentiation factors, interferons, chemotactic proteins or an unspecific immunomodulating agent, may also be included.

The type of dosage is determined by the attending physician according to the clinical factors. The skilled worker knows that the type of dosage depends on various factors such as, for example, body size or weight, body surface area, age, sex or general health of the patient, or else on the agent to be specially administered, duration and type of administration, and on other medicaments which may be administered in parallel. A typical dose may be, for example, in a range between 0.001 and 1000 µg, with doses being conceivable below and above this exemplary range, especially when taking into account the abovementioned factors. If the composition of the invention is administered regularly, the unit dose per day should generally be in a range between 1 µg and 10 mg. The active compounds in these preparations are usually present at a concentration of more than 10 µg/ml of a physiological buffer. However, they may also be present in solid form at a concentration of from 0.1 to 99.5% by weight of the total mixture. In general, it has proven advantageous to administer the active compound(s) in total amounts of from about 0.001 to 100 mg/ kg, preferably in total amounts of from about 0.01 to 10 mg/kg, of body weight per 24 hours, where appropriate as continuous infusion or in the form of a plurality of individual doses, in order to achieve the desired result. If the composition is administered intravenously, the unit dose per kilogram of body weight per day should be in a range between 1 µg and 10 mg. The medicament may be administered topically, locally or systemically.

Finally, particular preference is given according to the invention to a process in which the product is an enantiomerically pure alcohol.

The invention also relates to a ligand which specifically binds the polypeptide of the invention, which ligand is neither a substrate of said polypeptide, nor a cofactor thereof, nor a product converted thereby.

The term "specifically binds" means according to the invention that the ligand does not or essentially does not cross react with other polypeptides, including those having a similar primary sequence or a similar three-dimensional structure. Cross reactivity may be determined by processes known in the prior art (cf. Harlow and Lane "Antibodies, A Laboratory Manual", CSH Press, Cold Spring Harbor, 1988). To this end, it is possible to use, for example, competitive assays, for example turbidimetric tests, in which the ligand is incubated together with the labeled polypeptide of the invention and a polypeptide competing therewith, it being possible for the latter to be used at different concentrations.

In a preferred embodiment, the ligand of the invention is an antibody or a fragment or derivative thereof, an aptamer, or a low-molecular weight substance.

Antibody fragments comprise Fv, Fab and $F(ab')_2$ fragments. The derivatives include scFvs (Harlow and Lane, loc. cit.). Antibodies may be of polyclonal or monoclonal origin. In a particularly preferred embodiment of the receptor of the invention, said receptor is a monoclonal antibody.

According to the invention, "low molecular weight substances" are naturally occurring or artificially produced molecules having a molecular weight of from about 250 to 1000 Da, preferably 300 to 750 Da, particularly

preferably 400 to 600 Da, or are modified molecules of said molecular weight, which have been derived from natural substances.

The claimed invention furthermore comprises a primer having a sequence depicted in Table 1.

In addition, the invention relates to a primer pair having sequences depicted in Table 1, with the first primer of said primer pair serving as a forward primer and the second primer of said primer pair serving as a reverse primer to amplify a DNA sequence.

The primer of the invention (in combination with a further suitable primer, preferably a further suitable primer listed in Table 1) and the primer pair of the invention may be used for amplification of the sequences of the invention, preferably by means of PCR or LCR. The primers and primer pairs, respectively, have been selected with great care from a multiplicity of potentially possible primers. Besides amplification of the nucleic acid sequences of the invention, they also allow amplification of sequences which encode enzymes of the prior art, and are thus versatile.

The invention further relates to a kit comprising

the polypeptide of the invention;

the nucleic acid molecule of the invention;

the vector of the invention;

the host of the invention;

the ligand of the invention;

the reaction system of the invention;

at least one primer of the invention; and/or

at least one primer pair of the invention.
The components of the kit of the invention may be packaged individually or partly together in suitable vessels. The components may be present in the kit of the invention, for example, in freeze-dried form or, for example, in solution, with suitable solvents including in particular aqueous solvents such as buffered solutions, for example phosphate-buffered solutions.

The kits of the invention may be used in many different ways. For example, they may serve to identify further alcohol dehydrogenases or nucleic acids encoding these, with preference being given to using the primers of the invention. In other embodiments, the kits of the invention may be used for industrial production of the enzyme of the invention or of the products converted by said enzyme. In these embodiments, preference would be given to using the host of the invention or the reaction system of the invention.
In the Figures:

Fig. depicts the prior art via the resolution of the racemate: at least 4-4 steps

Fig. depicts an overview of cluster 2 (= primer group 2), based on 33 sequences

Fig. 3: depicts PCR typing with primer group 2, using various pools

The examples illustrate the invention.Example 1: Clustering of ADHs and primer design

Strains were prioritized from an extensive proprietary strain collection and grown in liquid culture after carrying out viability and purity checks. Harvested cell

pellets served as starting material for genetic screening. Primers for genetic screening for alcohol dehydrogenase genes were constructed and then tested on the basis of prepared genomic DNA of selected microbial isolates with the aid of PCR. NAD- or NADP-dependent alcohol dehydrogenases are classified as long-chain, medium-chain and short-chain ADHs. Since sequence heterogeneity within these groups is substantial, said groups were grouped in clusters based on sequence analyses. The long-chain ADHs were divided into three clusters, the medium-chain ADHs in 4 clusters and the short-chain ADHs in three clusters. Subsequently, in each case four degenerated primer sets per cluster were constructed which differ in the utilization of specific codons (codon usage) but which are directed against the same sequence motifs of the clusters.
Example 2:

Genetic screening for long-chain alcohol dehydrogenases

The long-chain ADHs were divided on the basis of sequence analyses into three clusters and the primers were constructed and tested with an analogous procedure. However, despite expectations to the contrary, no PCR tags assignable to this group were amplified. Example 3:

Genetic screening for medium-chain alcohol dehydrogenases

Primers directed against medium-chain ADHs were designed as follows: the medium-chain ADHs were divided based on sequence analysis into four clusters. Subsequently, in each case four degenerated primer sets were constructed which differ by the selected codon usage. This will be illustrated graphically and by way of example in Figure 2 on the basis of the group of organisms for determining the primer group 2. The primer sets were selected on the basis of conserved regions in 33 different alcohol dehydrogenase sequences.

These primer groups, for example primer group 2, were subsequently used for investigating various pools (containing genomic DNA from microorganisms). Using this primer set, it was possible to amplify, clone and sequence novel partial medium-chain ADH sequences. The corresponding result of this PCR typing is depicted below in Figure 3. As documented, inter alia, by lanes 1, 2 and 10 in Figure 3, in each case here gene sequences were found which indicate an alcohol dehydrogenase activity, owing to the gene sequence corresponding to known genes of ADH enzymes. Overall, further gene sequences with potential alcohol dehydrogenase activity were identified. The identity of the sequence tags found with already known ADHs was between 51 - 99%.

Example 4:

Genetic screening for special medium-chain alcohol dehydrogenases, with analogy to alcohol dehydrogenases from *Rhodococcus* strains

Owing to the interesting properties of the known *Rhodococcus erythropolis* (S)-alcohol dehydrogenase (S-Re-ADH; this enzyme is characterized by stereoselective conversion of a broad spectrum of ketones and ketoesters to the corresponding hydroxy compounds) which likewise belongs to the medium-chain alcohol dehydrogenases, and also of other alcohol dehydrogenases obtained from *Rhodococcus* strains, the question as to whether it is possible to identify novel ADH sequences exhibiting a relatively high similarity to this sequence with the aid of genetic screening, was looked into. The driving force here is the assumption that novel ADHs whose sequences share a high identity with the S-Re-ADH sequence could likewise possess interesting properties. For example, such novel ADHs could possess on the one hand the proven properties of S-Re-ADH but, on the other hand, for example, could have a modified substrate spectrum or increased expression performance. In order to answer the above question, comparative sequence analyses with the amino acid sequence of this S-Re-ADH were

carried out first. These analyses revealed that S-Re-ADH is a representative of cluster 1 of the medium-chain ADHs. Furthermore, a group consisting of 5 protein sequences, which includes S-Re-ADH, was found within this cluster. Starting from these 5 sequences, degenerated primers were constructed and assayed, taking into account the codon usage, according to the procedure described above.

In order to reduce the number of PCRs to be carried out, pools consisting of 24 bacterial isolates were established and DNA was isolated. This DNA was used as template. Numerous sequence tags were amplified and sequenced. Analysis of the sequence tags translated into amino acid sequences revealed identities to the S-Re-ADH sequence of from about to Two full-length genes were isolated which are represented by one sequence tag and which exhibit 98% identity to S-Re-ADH at the amino acid sequence level. The novel ADHs are derived from the organism *Arthrobacter paraffineus* ATCC21317. The homology at the DNA level is 94%. Said full-length genes were isolated with the aid of a sequence homology approach.

Example 5:

Genetic screening for short-chain alcohol dehydrogenases

Moreover, 12 primer sets for the short-chain ADHs, which are directed against the three clusters of this group, were finally assayed. The template used was DNA which had been isolated from 5 isolates which, owing to their ADH activity, had reduced either 4-chloroacetophenone or 2-heptanone in the activity screening. The identity of the amino acid sequence tags to known short-chain ADH sequences is between and the vast majority of these sequences exhibiting an identity of less than to published sequences.

Table 1: sequences which were used for the screening of the DNA sequences encoding theac sof the invention

Name	Sequence 5' → 3'	Direction	Block
ADHM1:	AAAGCATGCGGCGTTTGYCAYACNGA	Forward	A
ADHM2:	CCAATGTTTCATCGCTTGATATGBNGTRATNCC	Reverse	C
ADHM3:	TGCGGCGTCTGCCAYACBGA	Forward	A
ADHM4:	GCTTCAGGGCGTGGTAGGBVGTVAYRCC	Reverse	C
ADHM5:	GCGGCGTCTGCCACWCSGA	Forward	A
ADHM6:	GCTTCAGGGCCTGGTAGGBSGTSAYSCC	Reverse	C
ADHM7:	AGCCTGCGGCGTCTGYCAYWCBGA	Forward	A
ADHM8:	GCTTCAGCGCCTGGTAGGBSGTSAYNCC	Reverse	C
ADHM9:	GCAGCTTGCGGCATGTGYCAYACNGA	Forward	A
ADHM10:	GCCCAAGCCGGTCGTAAYNCCRCANCC	Reverse	C
ADHM11:	GGCCTGCGGCATGTGYCAYACBGA	Forward	A
ADHM12:	CCCAAGCCGGTCGTGAYRMMRCAVCC	Reverse	C
ADHM13:	CCGGCATGTGCCACACSGA	Forward	A
ADHM14:	TGGCGGCCAGGCCSAYSSCSCC	Reverse	C
ADHM15:	GGCCTCCGGCATGTGYCAYACSGA	Forward	A
ADHM16:	TGGCGGCCAGGCCSAYNSCNCC	Reverse	C
ADHM17:	TTAAATGGTGCGGCATTTGYGGNWCNGA	Forward	A
ADHM18:	CAACTTAACAGCCAACATGCCDATNGKNCC	Reverse	D

ADHM19:	CAAGGTCAAGTGGTGCGGBATYTGYGG	Forward	A
ADHM20:	TGACGGCCAACATGCCRATNGKVCC	Reverse	D
ADHM21:	TGCGGCATCTGCGGSWCSGA	Forward	A
ADHM22:	CGAACTTGACGGCGAAGAKSCCGATSGKSC	Reverse	D
ADHM23:	CAAGGTCAAGTGGTGCGGNATCTGYGG	Forward	A
ADHM24:	CGGCGAAGATGCCGATSGKNCC	Reverse	D
ADHM25:	GATTGTTAGAGTTACAGCTACAGCTATTTGYGGNWSNGA	Forward	A
ADHM26:	TGAACGGCAAACAGGCCNAYNGGNCC	Reverse	D
ADHM27:	CGCCACCGCCATCTGYGGBWSBGA	Forward	A
ADHM28:	GACGGCGAACAGGCCNAYNGGVCC	Reverse	D
ADHM29:	CACCGCCATCTGCGGSWSSGA	Forward	A
ADHM30:	GGAGTGGACGGCGAACAKSCCSAYSGGSC	Reverse	D
ADHM31:	CGCCACCGCCATCTGYGGNWSBGA	Forward	A
ADHM32:	GACGGCGAACAGGCCSAYSGGNCC	Reverse	D
ADHM39	AGAAGAACTGGGCATTATGCCNCCNGGNYT	Forward	A
ADHM40	TGTATCAATTGTCGGTTGATAGCCNACRAARTCNA	Reverse	D
ADHM41	ACAACGTGGTCGTGTACGGNCCNTGGGG	Forward	
ADHM42	GATGGTGGGCTGGTAGCCNACRAARTCNA	Reverse	
ADHM43	GACAACGTCGTCGTCTACGGNCCNTGGGG	Forward	
ADHM44	AGCGCTTGATGGCGTGRTANGGNGT	Reverse	
ADHM45	GACAACGTCGTCGTCTACGGNCCNTGGGG	Forward	
ADHM46	GATGGTCGGCTGGTAGCCNACRAARTCNA	Reverse	

ADHS1:

What is claimed is:

1. A pe which has the biological activity of an dependent ac and which comprises or has one of the followinga acid csthe sce ofthesce ofthe sce ofr a sce which is at leastcal to the sce of , the sce ofthe sce of r a sce which is at leastcal to the sce of , the sce ofa sce which is at leastidentical to the sce of , the sce of a sequence which is at least cal to the sce of, the sce ofa sce which is at least cal to the sce of , the sce of a sce which is at least cal to the sce of , the sce of a sce which is at leastcal to the sce of S, the sce ofr a sce which is at least cal to the sce of , the sce of a sce which is at least cal to the sce of S, the sce ofa sce which is at least cal to the sce of , the sce ofa sce which is at leastcal to the sce of, the sce ofa sce which is at leastcal to the sce of, the sce ofa sce which is at least cal to the sce of, the sce of a sce which is at leastcal to the sce of, the sce ofa sce which is at leastcal to the sce of , the sce ofa sce which is at leastcal to the sce of, the sce of a sequence which is at least cal to the sce of, the sce ofa sce which is at least cal to the sce of, the sce ofa sce which is at least cal to the sce ofthe sce of a sce which is at leastcal to the sce ofthe sce ofa sce which is at leastcal to the sce of, the sce ofa sce which is at least cal to the sequence of the sce ofa sce which is at least cal to the sce ofthe sce ofa sce which is at leastcal to the sce of, the sce ofa sce which is at least cal to the sce of the sce of a sce which is at least 70cal to the sce ofthe sce ofr a sce which is at leastcal to the sce of, the sce of a sce which is at least cal to the sce ofthe sce of r a sce which is at least cal to the sce ofthe sce ofthe sce of
2. A nucleic acid molecule, which encodes the polypeptide as claimed in claim 1.

3. A nucleic acid molecule, which is complementary to the nucleic acid molecule as claimed in claim 2.

4. A vector, which comprises the nucleic acid molecule as claimed in claim 2 or 3.

5. A nonhuman host, which comprises the polypeptide as claimed in claim 1 or the nucleic acid molecule as claimed in claim 2 or 3 or the vector as claimed in claim 4.

6. The host as claimed in claim 5, which is a cell.

7. The host as claimed in claim 5, which is a transgenic nonhuman animal.

8. The host as claimed in any of claims 5 to 7, which has a further dehydrogenase suitable for cofactor regeneration or a nucleic acid molecule encoding said dehydrogenase.

9. The host as claimed in claim 8, in which the dehydrogenase suitable for cofactor regeneration is a formate dehydrogenase or a glucose dehydrogenase.

10. A reaction system, comprising an organic compound which is a substrate of a dehydrogenase, the polypeptide as claimed in claim 1, the vector as claimed in claim 4 or the host as claimed in any of claims 5 to 9 and, where appropriate, a cofactor for the polypeptide as claimed in claim 1.

11. The reaction system as claimed in claim 10, in which the organic compound which is a substrate of a dehydrogenase is a carbonyl compound.

12. The reaction system as claimed in claim 11, in which the carbonyl compound is an aldehyde or a ketone.

13. The reaction system as claimed in claim 12, in which the ketone is an asymmetrically substituted ketone.

14. The reaction system as claimed in claim 10, in which the organic compound which is a substrate of a dehydrogenase is an alcohol.

15. The reaction system as claimed in claim 14, in which the alcohol is a primary alcohol or a chiral secondary alcohol.

16. The reaction system as claimed in any of claims 10 to 15, in which the cofactor is .

17. A process for preparing the polypeptide as claimed in claim 1 or of a polypeptide encoded by the nucleic acid molecule as claimed in claim 2, which process comprises growing the host as claimed in any of claims 5 to 9 and isolating said polypeptide.

18. A process for preparing the polypeptide as claimed in claim 1 or of a polypeptide encoded by the nucleic acid molecule as claimed in claim 2, which process comprises isolating said polypeptide from a body fluid or tissue sample of the host as claimed in any of claims 7 to 9.

19 A process for an organic compound which is a product of a dehydrogenase, which process comprises reacting an organic compound which is a substrate of a dehydrogenase with the polypeptide as claimed in claim 1, the host as claimed in any of claims 5 to 9 or by means of the reaction system as claimed in any of claims 10 to 16.

20. The process as claimed in claim 19, which further comprises the step of isolating the product of the reaction.

21. The process as claimed in claim 20, which further comprises processing the product to give a medicament.

22. The process as claimed in claim 20, further comprising the step of processing the product to give a secondary product.

23. The process as claimed in claim 22, further comprising the step of formulating the secondary product in the preparation of a medicament.

24. The process as claimed in any of claims 19 to 23, in which the product is an enantiomerically pure alcohol.

25. A ligand, which specifically binds the polypeptide as claimed in claim 1, which ligand is neither a substrate or cofactor of said polypeptide nor a product generated therefrom.

26. The ligand as claimed in claim 25, which is an antibody or a fragment or derivative thereof, an aptamer, or a low-molecular weight substance.

27. A primer, having a sequence depicted in Table 1.

28. A primer pair, having sequences depicted in Table 1, with the first primer of said primer pair serving as a forward primer and the second primer of said primer pair serving as a reverse primer to amplify a DNA sequence.

29. A kit, comprising

(a) the polypeptide as claimed in claim 1;

(b) the nucleic acid molecule as claimed in claim 2 or 3;

(c) the vector as claimed in claim 4;

(d) the host as claimed in any of claims 6 to 9;

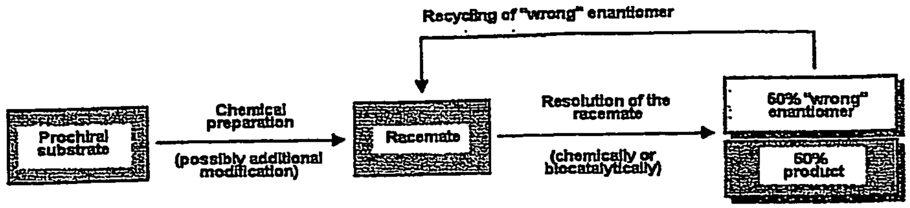
(e) the reaction system as claimed in any of claims 10 to 16;

(f) the ligand as claimed in claim 25 or 26;

(g) at least one primer as claimed in claim 27; and/or

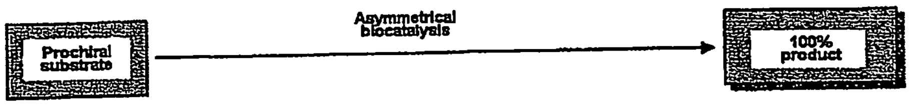
(h) at least one primer pair as claimed in claim 28.

- **Prior art via resolution of the racemate: at least 3-4 steps**



(1a)

- **Biocatalytic and sustainable concept: Asymmetrical biocatalysis**



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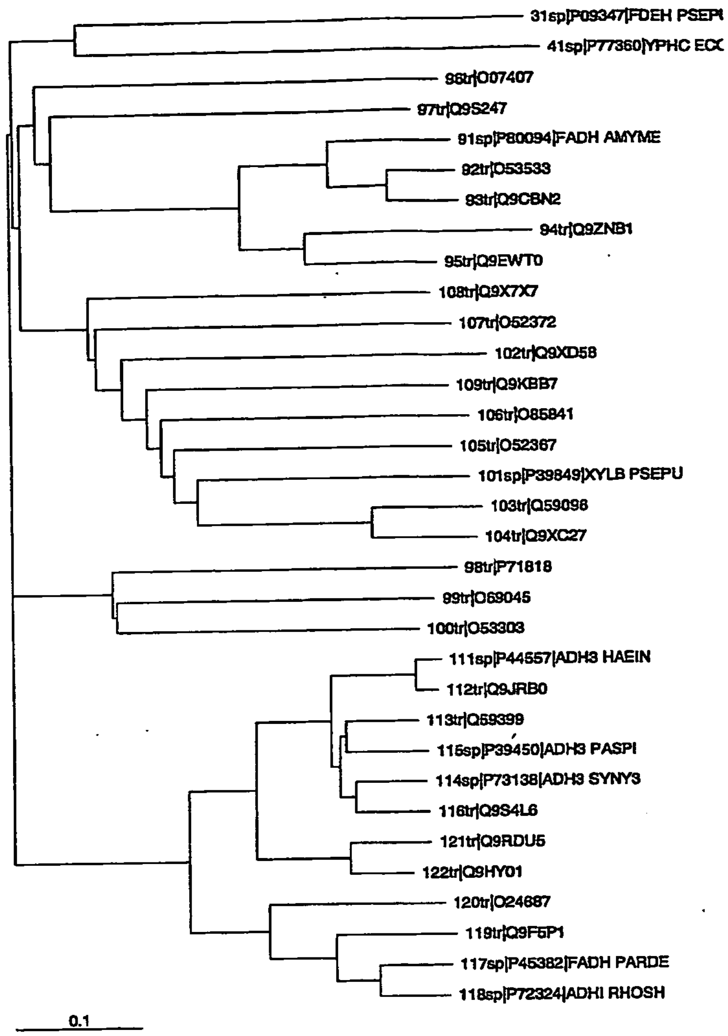

Fig. 2.

Overview of cluster 2 (= primer group 2), based on 33 sequences

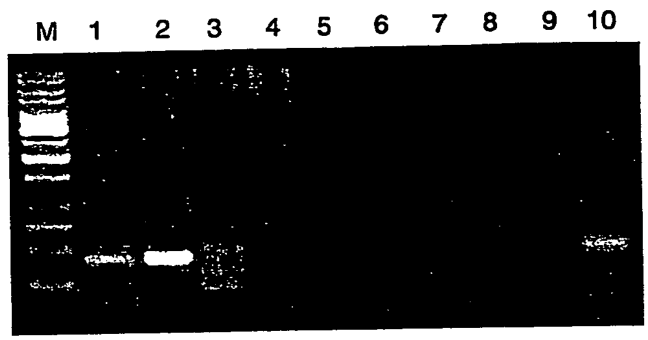

Fig. 3

PCR typing with primer group 2, using various pools

Lane occupation: M: Marker 1 kb DNA ladder; Lane 1: Pool 1 with primers ADHM9 + 10; Lane 2: Pool 1 with primers ADHM11 + 12; Lane 3: Pool 1 with primers ADHM13 + 14; Lane 4: Pool 1 with primers ADHM15 + 16; Lane 5: Pool 2 with primers ADHM 9 + 10; Lane 6: Pool 2 with primers ADHM11 + 12; Lane 7: Pool 2 with primers ADHM13 + 14; Lane 8: Pool 2 with primers ADHM15 + 16; Lane 9: Pool 3 with primers ADHM9 + 10; Lane 10: Pool 3 with primers ADHM11 + 12

Sequence Listing

<110> Degussa AG

<120> Novel alcohol dehydrogenases

<130> S-IPM-PAT/Dr. Re-kö - K1419 EP

<160> 68

<170> PatentIn version 3.1

<210> 1

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<212> PRT

<213> unknown

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<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0050197= Pseudomonas oleovorans; ZF0050294= Rhodococcus; ZF0050330= Bacillus; ZF0051303= Bacterium; ZF0051337= Methylomonas; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002852= Rhodococcus; ZF0050310= Arthrobacter paraffineus; ZF0002862= Streptomyces clavuligerus; ZF0050292= Bacterium; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0002437= Streptomyces; ZF0003712= Micromonospora; ZF0003765= Streptomyces; ZF0051305= Bacterium; ZF0003513= Actinomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0002332= Streptomyces diastatochromogenes; ZF0003768= Actinomyces; ZF0002379= Streptomyces coelescens; ZF0002351= Nonomuraea roseoviolacea; ZF0003769= Actinomyces;

<400> 1

Gly Pro Trp Gly Cys Gly Asn Cys Trp His Cys Ser Gln Gly Leu Glu
1 5 10 15

Asn Tyr Cys Ser Arg Ala Gln Glu Leu Gly Ile Asn Pro Pro Gly Leu
20 25 30

Gly Ala Pro Gly Ala Leu Ala Glu Phe Met Ile Val Asp Ser Pro Arg
35 40 45

His Leu Val Pro Ile Gly Asp Leu Asp Pro Val Lys Thr Val Pro Leu
50 55 60

Thr Asp Ala Gly Leu Thr Pro Tyr His Ala Ile Lys Arg Ser Leu Pro
65 70 75 80

Lys Leu Arg Gly Gly Ser Tyr Ala Val Val Ile Gly Thr Gly Gly Leu
85 90 95

Gly His Val Ala Ile Gln Leu Leu Arg His Leu Ser Ala Ser Thr Val
100 105 110

Ile Ala Leu Asp Val Ser Ala Asp Lys Leu Glu Leu Ala Thr Lys Val
115 120 125

Gly Ala His Glu Val Val Leu Ser Asp Lys Asp Ala Ala Glu Asn Val
130 135 140

Arg Lys Ile Thr Gly Ser Gln Gly Ala Ala Leu Val Leu Asp Phe Val
145 150 155 160

Gly Tyr

<210> 2

<211> 128

<212> PRT

<213> unknown

<220>

<221> source
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<400> 2

Gly Pro Trp Gly Cys Gly Asn Cys Trp His Cys Ser Gln Gly Leu Glu
1 5 10 15

Asn Tyr Cys Ser Arg Ala Gln Glu Leu Gly Ile Asn Pro Pro Gly Leu
20 25 30

Gly Ala Pro Gly Ala Leu Ala Glu Phe Met Ile Val Asp Ser Pro Arg
35 40 45

His Leu Val Pro Ile Gly Asp Leu Asp Pro Val Lys Thr Val Pro Leu
50 55 60

Thr Asp Ala Gly Leu Thr Pro Tyr His Ala Ile Lys Arg Ser Leu Pro
65 70 75 80

Lys Leu Arg Gly Gly Ser Tyr Ala Val Val Ile Gly Thr Gly Gly Leu
85 90 95

Gly His Val Thr Ile Gln Leu Leu Arg His Leu Ser Ala Ala Thr Val
100 105 110

Ile Ala Leu Asp Val Ser Ala Asp Lys Leu Glu Leu Ala Thr Lys Val
115 120 125

<210> 3

<211> 162

<212> PRT

<213> unknown

<220>

<221> source
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<400> 3

Gly Pro Trp Gly Cys Gly Arg Cys Trp His Cys Ala Gln Gly Leu Glu
1 5 10 15

Asn Tyr Cys Ser Arg Ala Arg Glu Leu Gly Ile Ala Pro Pro Gly Leu
20 25 30

Gly Ala Pro Gly Ala Ile Ala Glu Tyr Met Ile Val Asp Ser Pro Arg
35 40 45

His Leu Val Pro Ile Gly Asp Leu Asp Pro Val Thr Thr Val Pro Leu
50 55 60

Thr Asp Ala Gly Leu Thr Pro Tyr His Ala Ile Lys Arg Ser Leu Gly
65 70 75 80

Lys Leu Arg Ala Gly Ser Tyr Ala Val Val Ile Gly Thr Gly Gly Leu
85 90 95

Gly His Val Gly Ile Gln Leu Leu Arg His Leu Ser Pro Ala Arg Ile
100 105 110

Ile Ala Leu Asp Val Asn Asp Glu Lys Leu Ala Phe Ala Arg Glu Val
115 120 125

Gly Ala His Glu Thr Val Leu Ser Asn Ala Asp Ala Ala Ala Asn Val
130 135 140

Arg Lys Ile Thr Gly Ser Ala Gly Ala Ala Leu Val Leu Asp Phe Val
145 150 155 160

Gly Tyr

<210> 4

<211> 161

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 4

Gly Pro Trp Gly Cys Gly Ser Cys Trp His Cys Ser Gln Gly Leu Glu
1 5 10 15

Asn Tyr Cys Ser Arg Ala Lys Glu Leu Gly Ile Asn Pro Pro Gly Leu
20 25 30

Gly Ala Pro Gly Ala Leu Ala Glu Phe Met Ile Val Asp Ser Pro Arg

35 40 45

His Leu Val Pro Ile Gly Asp Leu Asp Pro Val Lys Thr Val Pro Leu
50 55 60
Thr Asp Ala Gly Leu Thr Pro Tyr His Ala Ile Lys Arg Ser Leu Pro
65 70 75 80

Lys Leu Arg Gly Gly Ala Tyr Ala Val Val Ile Gly Thr Gly Gly Leu
85 90 95

Gly His Val Ala Ile Gln Leu Leu Arg His Leu Ser Ala Ala Thr Val
100 105 110

Ile Ala Leu Asp Val Ser Ala Asp Lys Leu Val Leu Ala Thr Lys Val
115 120 125

Gly Ala His Glu Val Val Leu Ser Asp Lys Asp Ala Ala Glu Asn Val
130 135 140

Arg Arg Ile Thr Gly Ser Gln Gly Ala Ala Leu Val Leu Asp Phe Val
145 150 155 160

Gly

<210> 5

<211> 70

<212> PRT

<213> unknown

<220>

<221> source
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<400> 5

Gly Pro Trp Gly Cys Gly Thr Cys Val Lys Cys Ala Glu Gly Lys Glu
1 5 10 15

Asn Tyr Cys Leu Arg Ala Lys Glu Leu Gly Ile Ala Pro Pro Gly Leu
20 25 30

Gly Ser Pro Gly Ala Met Ala Glu Tyr Met Ile Val Asp Asp Pro Arg
35 40 45

His Leu Val Pro Leu Gly Gly Leu Asp Pro Val Gln Ala Val Pro Leu
50 55 60

Thr Asp Ala Gly Leu Thr
65 70

<210> 6

<211> 94

<212> PRT

<213> unknown

<220>
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<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821= Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 6

Cys His Thr Asp His His Ile Val Thr Gly Ala Thr Pro Met Pro Ser
1 5 10 15

Phe Pro Val Met Gly Gly His Glu Gly Ser Gly Val Ile Thr Lys Leu
20 25 30

Gly Pro Glu Val Lys Gly Leu Glu Val Gly Asp His Val Val Leu Ser

35 40 45

Phe Ile Pro Ala Cys Gly Thr Cys Pro Ala Cys Ser Ala Gly His Gln
50 55 60

Asn Leu Cys Asp Leu Gly Met Gly Leu Leu Ser Gly Gln Ala Ile Ser
65 70 75 80

Asp Gly Thr Tyr Arg Ile Gln Ala Arg Gly Glu Asn Val Ile
85 90

<210> 7

<211> 92

<212> PRT

<213> unknown

<220>

<221> source
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<400> 7

Cys His Thr Asp Asp His Ala Val Thr Gly Asp Leu Ala Val Pro Leu
1 5 10 15

Pro Val Ile Gly Gly His Glu Gly Ala Gly Ile Val Glu Lys Val Gly
20 25 30

Pro Gly Val Arg Asp Val Glu Val Gly Asp His Val Val Leu Ser Phe
35 40 45

Ile Pro Ser Cys Gly Arg Cys Arg Trp Cys Ala Val Gly Gln Ser Asn
50 55 60

Leu Cys Asp Leu Gly Ala Ile Leu Met Ala Gly Ala Gln Val Asp Gly
65 70 75 80

Thr Tyr Arg Ala Thr Ala Arg Gly His Asp Val Gly
85 90

<210> 8

<211> 92

<212> PRT

<213> unknown

<220>

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<400> 8

Cys His Thr Asp Asp His Ala Val Thr Gly Asp Leu Ala Val Pro Leu
1 5 10 15

Pro Val Ile Gly Gly His Glu Gly Ala Gly Ile Val Glu Lys Val Gly
20 25 30

Pro Gly Val Arg Asp Val Glu Val Gly Asp His Val Val Leu Ser Phe
35 40 45

Ile Pro Ser Cys Gly Arg Cys Arg Trp Cys Ala Val Gly Gln Ser Asn
50 55 60

Leu Cys Asp Leu Gly Ala Ile Leu Met Ala Gly Ala Gln Val Asp Gly
65 70 75 80

Thr Tyr Arg Ala Thr Ala Arg Gly His Asp Val Gly
85 90

<210> 9

<211> 92

<212> PRT

<213> unknown

<220>

<221> source
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<400> 9

Cys His Thr Asp Asp His Ala Val Thr Gly Asp Leu Ala Val Pro Leu
1 5 10 15

Pro Val Ile Gly Gly His Glu Gly Ala Gly Ile Val Glu Lys Val Gly
20 25 30

Pro Gly Val Arg Asp Val Glu Val Gly Asp His Val Val Leu Ser Phe
35 40 45

Ile Pro Ser Cys Gly Arg Cys Arg Trp Cys Ala Val Gly Gln Ser Asn
50 55 60

Leu Cys Asp Leu Gly Ala Ile Leu Met Ala Gly Ala Gln Val Asp Gly
65 70 75 80

Thr Tyr Arg Ala Thr Ala Arg Gly His Asp Val Gly
85 90

<210> 10

<211> 92

<212> PRT

<213> unknown

<220>

<221> source
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Cys His Thr Asp Asp His Ala Val Thr Gly Asp Leu Ala Val Pro Leu
1               5                   10                  15

Pro Val Ile Gly Gly His Glu Gly Ala Gly Ile Val Glu Lys Val Gly
            20                  25                  30

Pro Gly Val Arg Asp Val Glu Val Gly Asp His Val Val Leu Ser Phe
        35                  40                  45

Ile Pro Ser Cys Gly Arg Cys Arg Trp Cys Ala Val Gly Gln Ser Asn
    50                  55                  60

Leu Cys Asp Leu Gly Ala Ile Leu Met Ala Gly Ala Arg Val Asp Gly
65                  70                  75                  80

Thr Tyr Arg Ala Thr Ala Arg Gly His Asp Val Gly
                85                  90
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<210> 11

<211> 92

<212> PRT

<213> unknown

<220>

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Cys His Thr Asp Asp His Ala Val Thr Gly Asp Leu Ala Val Pro Leu
1               5                   10                  15

Pro Val Ile Gly Gly His Glu Gly Ala Gly Ile Val Glu Lys Val Gly
            20                  25                  30

Pro Gly Val Arg Asp Val Glu Val Gly Asp His Val Val Leu Ser Phe
        35                  40                  45

Ile Pro Ser Cys Gly Arg Cys Arg Trp Cys Ala Val Gly Gln Ser Asn
    50                  55                  60

Leu Cys Asp Leu Gly Ala Ile Leu Met Ala Gly Ala Gln Val Asp Gly
65                  70                  75                  80

Thr Tyr Arg Ala Thr Ala Arg Gly His Asp Val Gly
                85                  90
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<210> 12

<211> 93
<212> PRT

<213> unknown

<220>

<221> source

<223> ZF0050310= Arthrobacter paraffineus

<400> 12

Cys His Thr Asp Leu Phe Thr Lys Ser Val Leu Pro Glu Arg Leu Gly
1 5 10 15

Pro Cys Val Phe Gly His Glu Gly Ala Gly Val Val Glu Ala Val Gly
20 25 30

Ser Ser Ile Asp Ser Ile Ala Pro Gly Asp His Val Leu Leu Ser Tyr
35 40 45

Arg Ser Cys Gly Val Cys Arg Gln Cys Leu Ser Gly His Arg Ala Tyr
50 55 60

Cys Glu Ser Ser His Gly Leu Asn Ser Ser Gly Ala Arg Thr Asp Gly
65 70 75 80

Ser Thr Pro Val Arg Arg Ser Gly Thr Pro Ile Arg Ser
85 90

<210> 13

<211> 93

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0002333=Rhodoccocus erythropolis

<400> 13

Cys His Thr Asp Leu Phe Thr Lys Thr Val Leu Pro Glu Lys Leu Gly
1 5 10 15

Pro Cys Val Phe Gly His Glu Gly Ala Gly Val Val Gln Ala Val Gly
20 25 30

Ser Ser Ile Asp Asn Ile Ala Ala Gly Asp His Val Leu Leu Ser Tyr
35 40 45

Arg Ser Cys Gly Val Cys Arg Gln Cys Leu Ser Asp His Arg Ala Tyr
50 55 60

Cys Glu Ser Ser His Gly Leu Asn Ser Ser Gly Ala Arg Thr Asp Gly
65 70 75 80

Ser Thr Pro Val Arg Arg Asn Gly Thr Pro Ile Arg Ser
85 90

<210> 14

<211> 120

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0051303= Bacterium; ZF0051337= Methylomonas; ZF0002862= Streptomyces clavuligerus; ZF0050292= Bacterium; ZF0051305= Bacterium; ZF0003513= Actinomyces; ZF0002351= Nonomuraea roseoviolacea; ZF0003769= Actinomyces; ZF0002017= Streptomyces; ZF0051306= Bacterium; ZF0002016= Streptomyces; ZF0003504= Actinomyces; ZF0006073= Streptomyces; ZF0003770= Actinomyces; ZF0002352= Actinoplanes italicus; ZF0002378= Streptomyces aureomonopodiales; ZF0006089= Streptomyces; ZF0006106= Streptomyces; ZF0051325= Bacterium; ZF0006108= Streptomyces; ZF0002440= Streptomyces; ZF0051302= Bacterium; ZF0003532= Actinomyces; ZF0003548= Nocardiaform;

<400> 14

Cys Gly Thr Asp Arg Glu Ile Ala Ser Gly Ile Tyr Gly Trp Ala Pro
1 5 10 15

Pro Gly Arg Glu His Leu Val Leu Gly His Glu Ser Leu Gly Arg Val
20 25 30

Arg Thr Ala Pro Asp Gly Ser Gly Phe Ala Ala Gly Asp Leu Val Val
35 40 45

Gly Ile Val Arg Arg Pro Asp Pro Val Pro Cys Gly Ala Cys Ala His
50 55 60

Gly Glu Phe Asp Met Cys Arg Asn Gly Glu Tyr Val Glu Arg Gly Ile
65 70 75 80

Lys Gln Ile Asp Gly Tyr Gly Ser Thr Ser Trp Val Val Asp Ala Asp
85 90 95

Tyr Thr Val Lys Leu Asp Pro Ala Leu Thr Glu Val Gly Val Leu Met

100 105 110

Glu Pro Thr Thr Val Leu Gly Gln
115 120

<210> 15

<211> 140

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0051303= Bacterium; ZF0051337= Methylomonas; ZF0002862= Streptomyces clavuligerus; ZF0050292= Bacterium; ZF0051305= Bacterium; ZF0003513= Actinomyces; ZF0002351= Nonomuraea roseoviolacea; ZF0003769= Actinomyces; ZF0002017= Streptomyces; ZF0051306= Bacterium; ZF0002016= Streptomyces; ZF0003504= Actinomyces; ZF0006073= Streptomyces; ZF0003770= Actinomyces; ZF0002352= Actinoplanes italicus; ZF0002378= Streptomyces aureomonopodiales; ZF0006089= Streptomyces; ZF0006106= Streptomyces; ZF0051325= Bacterium; ZF0006108= Streptomyces; ZF0002440= Streptomyces; ZF0051302= Bacterium; ZF0003532= Actinomyces; ZF0003548= Nocardiaform;

<400> 15

Cys Gly Thr Asp Leu His Ile Arg Ser Trp Asp Gly Trp Ala Gln Lys
1 5 10 15

Thr Ile Ala Thr Pro Leu Thr Leu Gly His Glu Phe Val Gly Glu Val
20 25 30

Val Glu Thr Gly Arg Asp Val Thr Asp Ile Gln Val Gly Asp Leu Val
35 40 45

Ser Gly Glu Gly His Leu Val Cys Gly Lys Cys Arg Asn Cys Leu Ala
50 55 60

Gly Arg Arg His Leu Cys Arg Ala Thr Val Gly Leu Gly Val Gly Arg
65 70 75 80

Asp Gly Ala Phe Ala Glu Tyr Val Val Leu Pro Ala Ser Asn Val Trp
85 90 95

Val His Arg Val Pro Val Asp Leu Asp Val Ala Ala Ile Phe Asp Pro
100 105 110

Phe Gly Asn Ala Val His Thr Ala Leu Ser Phe Pro Leu Val Gly Glu

115 120 125

Asp Val Leu Val Thr Gly Ala Gly Thr Ile Gly Ile
130 135 140

<210> 16

<211> 138

<212> PRT

<213> unknown

<220>

<221> source
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<400> 16

Gly Leu Thr Ile Gly His Glu Pro Val Gly Val Ile Glu Lys Leu Gly
1 5 10 15

Ser Ala Val Thr Gly Tyr Arg Glu Gly Gln Arg Val Ile Ala Gly Ala
20 25 30

Ile Cys Pro Asn Phe Asn Ser Tyr Ala Ala Gln Asp Gly Ala Pro Ser
35 40 45

Gln Asp Gly Ser Tyr Leu Val Ala Ser Gly Ala Cys Gly Cys His Gly
50 55 60

Tyr Arg Ala Thr Ala Gly Trp Arg Phe Gly Asn Ile Ile Asp Gly Ala
65 70 75 80

Gln Ala Glu Tyr Leu Leu Val Pro Asp Ala Gln Gly Asn Leu Ala Pro
85 90 95

Val Pro Asp Asn Leu Ser Asp Glu Gln Val Leu Met Cys Pro Asp Ile
100 105 110

Met Ser Thr Gly Phe Lys Gly Ala Glu Asn Ala His Ile Arg Ile Gly
115 120 125

Asp Thr Val Ala Val Phe Ala Gln Gly Pro
130 135

<210> 17

<211> 144

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050197= Pseudomonas oleovorans; ZF0050294= Rhodococcus; ZF0050330= Bacillus, ZF0002852= Rhodococcus; ZF0050310= Arthrobacter paraffineus; ZF0002437= Streptomyces; ZF0003712= Micromonospora; ZF0003765= Streptomyces; ZF0002332= Streptomyces diatsatochromogenes; ZF0003768= Actinomyces; ZF0002379= Streptomyces coelescens; ZF0002443= Streptomyces; ZF0002442= Streptomyces; ZF0002436= Streptomyces; ZF0050994= Bacterium; ZF0050992= Bacterium; ZF0050442= Bacterium; ZF0002049= Streptomyces; ZF0006069= Streptomyces; ZF0006075= Streptomyces; ZF0004724= Nocardiaform; ZF0002392= Actinoplanes nipponensis; ZF0002356= Actinoplanes brasiliensis; ZF0003501= Actinomyces; ZF0051322= Bacterium; ZF0006078= Streptomyces; ZF0006092= Streptomyces; ZF0006090= Streptomyces; ZF0006084= Streptomyces; ZF0006068= Streptomyces; ZF0050284= Rhodococcus; ZF0050028= Agrobacterium tumefaciens; ZF0003540= Actinomyces; ZF0003528= Actinomyces; ZF0003529= Actinomyces;

<400> 17

Cys Gly Thr Asp Leu His Ile Leu Gly Gly Asp Val Pro Glu Val Thr
1 5 10 15

Asp Gly Arg Ile Leu Gly His Glu Ala Val Gly Thr Val Val Glu Val
20 25 30

Gly Asp Gly Val Gln Thr Leu Ala Pro Gly Asp Arg Val Leu Val Ser
35 40 45

Cys Val Thr Ala Cys Gly Thr Cys Arg Phe Cys Arg Glu Ser Arg Tyr
50 55 60

Gly Gln Cys Leu Gly Gly Gly Gly Trp Ile Leu Gly His Leu Ile Asp
65 70 75 80

Gly Thr Gln Ala Glu Leu Val Arg Val Pro Tyr Ala Asp Asn Ser Thr
85 90 95

His Arg Ile Pro Asp Gly Val Ser Asp Glu Gln Met Leu Met Leu Ala
100 105 110

Asp Ile Leu Pro Thr Ser Tyr Glu Val Gly Val Leu Asn Gly Cys Leu
115 120 125

Arg Pro Ala Asp Val Val Val Ile Ile Gly Ala Asp Asp Arg Pro Leu
130 135 140

<210> 18

<211> 73

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 18

Val Asp Val Val Val Asp Asn Ala Gly Phe Gly Thr His Gly Ala Phe
1 5 10 15

Val Asp Glu Asp His Glu Arg Val Thr Ser Glu Ile Gln Leu Asn Ile
20 25 30

Ala Thr Leu Val Glu Leu Thr His Thr Phe Pro Pro Asp Leu Leu Thr
35 40 45

```
Gly Arg Gly Ala Leu Val Asn Ile Ala Ser Thr Ala Ser Phe Gln Pro
    50                  55                  60

Thr Pro Gly Met Ala Val Tyr Cys Ala
65                  70


<210>  19

<211>  75

<212>  PRT

<213>  unknown

<220>

<221>  source
<223>  ZF0050310= Arthrobacter paraffineus

<400>  19

Val Asp Val Val Val His Asn Ala Gly Phe Gly Thr His Gly Ala Phe
1               5                   10                  15

Val Asp Glu Asp Leu Glu Arg Val Thr Ser Glu Ile Gln Leu Asn Ile
            20                  25                  30

Ala Thr Leu Val Glu Leu Thr His Thr Phe Leu Pro Asp Leu Leu Thr
        35                  40                  45

Gly Arg Gly Ala Leu Val Asn Ile Ala Ser Thr Ala Ser Phe Gln Pro
    50                  55                  60

Thr Pro Gly Met Ala Val Tyr Cys Ala Thr Lys
65                  70                  75


<210>  20

<211>  79

<212>  PRT

<213>  unknown

<220>

<221>  source
<223>  ZF0003535= Actinomyces

<400>  20

Arg Val Asp Val Val Val His Asn Ala Ala Ile Thr Gln Lys Ala Thr
```

1 5 10 15

Phe Arg Asp Ile Thr Pro Ala Asp Phe Glu Arg Ile Leu Arg Val Asn
20 25 30

Leu Thr Gly Val Phe Asn Leu Ser Gln Ala Val Ile Pro Leu Met Ile
35 40 45

Gln Arg Gly Gly Gly Ser Ile Val Ser Ile Ser Ser Leu Ser Ala Gln
50 55 60

Asn Gly Gly Gly Ile Phe Gly Gly Ala His Tyr Cys Ala Thr Lys
65 70 75

<210> 21

<211> 76

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0003535= Actinomyces

<400> 21

Val Asp Val Val Val Asp Asn Ala Gly Leu Ala Leu Gly Thr Ala Pro
1 5 10 15

Ala Pro Gln Val Pro Leu Lys Asp Trp Gln Thr Met Val Asn Thr Asn
20 25 30

Ile Thr Gly Leu Leu Asn Ile Thr His His Leu Leu Pro Thr Leu Ile
35 40 45

Asp Arg Lys Gly Ile Val Val Asn Leu Ser Ser Val Ala Ala His Tyr
50 55 60

Pro Tyr Thr Gly Gly Asn Val Tyr Cys Ala Ser Lys
65 70 75

<210> 22

<211> 72

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 22

Gln Gly Ile Gly Tyr Ala Thr Ala Lys Arg Leu Ile Ser Leu Gly Ala
1 5 10 15

Thr Val Ala Ile Gly Asp Ile Asp Glu Ala Thr Leu Ala Arg Ala Ala
20 25 30

Lys Asp Leu Gly Ile Arg Thr Phe Gly Arg Leu Asp Val Thr Asp Pro
35 40 45

Ala Ser Phe Phe Asp Phe Leu Asp Thr Val Glu Gly Glu Leu Gly Pro
50 55 60

Ile Asp Val Leu Ile Asn Asn Ala
65 70

<210> 23

<211> 75

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 23

Gln Arg Ile Gly Leu Glu Ile Ala Arg Thr Phe Ile Lys Glu Gly Ala
1 5 10 15

Thr Val Val Leu Gly Asp Ile Asn Glu Thr Val Gly Thr Ala Ala Val
20 25 30

Ala Glu Leu Gly Gly Glu Ser Val Ala Arg Phe Ala Ser Cys Asp Val
35 40 45

Arg Asp Ser Gly Gln Val Glu Ala Met Leu Asp Leu Ala Glu Ser Ala
50 55 60

Phe Gly Pro Val Asp Val Met Met Asn Asn Ala
65 70 75

<210> 24

<211> 72

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 24

Gln Gly Ile Gly Tyr Gln Thr Ala Lys Glu Leu Ile Arg Arg Gly His
1 5 10 15

Arg Val Ala Ile Gly Asp Ile Asp Glu Ala Arg Ala Lys Glu Thr Ala
20 25 30

Ala Glu Leu Gly Val Lys Val Val Thr Arg Leu Asp Val Thr Asp Pro
35 40 45

Asp Ser Phe Lys Asp Phe Leu Asp Leu Val Glu Gly Asp Leu Gly Pro
50 55 60

Leu Asp Val Leu Ile Asn Asn Ala
65 70

<210> 25

<211> 74

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 25

Gly Ile Gly Leu Glu Ile Ala Arg Thr Phe Ile Lys Glu Gly Ala Thr
1 5 10 15

Val Val Leu Gly Asp Ile Asn Glu Thr Val Gly Thr Ala Ala Val Ala
20 25 30

Glu Leu Gly Gly Glu Ser Val Ala Arg Phe Ala Ser Cys Asp Val Arg
35 40 45

Asp Ser Gly Gln Val Glu Ala Met Leu Asp Leu Ala Glu Ser Ala Phe
50 55 60

Gly Pro Val Asp Val Ile Val Asn Asn Ala
65 70

<210> 26

<211> 74

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 26

Ile Gly Leu Glu Ile Ala Arg Thr Phe Ile Lys Glu Gly Ala Thr Val
1 5 10 15

Val Leu Gly Asp Ile Asn Glu Thr Val Gly Thr Ala Ala Val Gly Glu
20 25 30

Leu Gly Gly Glu Ser Val Ala Arg Phe Ala Ser Cys Asp Val Arg Asp
35 40 45

Ser Gly Gln Val Glu Ala Met Leu Asp Leu Ala Glu Ser Ala Phe Gly
50 55 60

Pro Val Asp Val Met Val Asn Asn Ala Gly
65 70

<210> 27

<211> 62

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0002333= Rhodococcus erythropolis

<400> 27

Val Pro Val Ala Val Val Asp Leu His Ile Glu Ser Ala Lys Glu Thr
1 5 10 15

Val Ala Leu Ile Glu Ser Gln Tyr Gly Thr Pro Ala Leu Ala Leu Glu
20 25 30

Ala Asp Val Arg Asp Arg Ala Ala Val Ser Ala Ala Phe Glu Ala Thr
35 40 45

Val Ala Glu Trp Gly Arg Phe Asp Tyr Leu Val Asn Asn Ala
50 55 60

<210> 28

<211> 74

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0002333= Rhodococcus erythropolis

<400> 28

Leu Gly Arg Glu Ile Ala Leu Lys Leu Ala Ser Glu Gly Ala Ser Val
1 5 10 15

Val Val Asn Asp Leu Asp Pro Glu Pro Ala Ala Gln Thr Glu Arg Asp
20 25 30

Ile Lys Ala Thr Gly Gly Gln Ala Val Ser Cys Val Gly Ser Val Ala
35 40 45

Glu Asp Gly Phe Ala Glu Arg Phe Val Asn Thr Ala Val Glu Ser Phe
50 55 60

Gly Gly Leu Asp Val Met Val Asn Asn Ala
65 70

<210> 29

<211> 76

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0002333= Rhodococcus erythropolis

<400> 29

Ala Gly Leu Gly Val Glu Phe Ala His Arg Phe Ala Ala Arg Gly Ala
1 5 10 15

Asn Leu Val Leu Val Ala Arg Arg Ala Asp Arg Leu Glu Ala Leu Ala
20 25 30

Thr Glu Leu Arg Val Ala His Gly Ile Thr Val Thr Val Leu Pro Ala
35 40 45

Asp Leu Ala Ala Pro Gly Val Gly Ala Thr Leu His Gln Glu Leu Thr
50 55 60

Ser Arg Gly Ile Thr Val Thr Ser Leu Ile Asn Asn
65 70 75

<210> 30

<211> 72

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0003535= Actinomyces

<400> 30

Pro Ala Asp Gly Tyr Gln Thr Ala Lys Glu Leu Ile Arg Arg Gly His
1 5 10 15

Arg Val Ala Ile Val Asp Ile Asp Glu Ala Arg Ala Lys Gly Ala Ala
20 25 30

Ala Glu Leu Gly Val Lys Val Val Thr Arg Leu Asp Val Thr Glu Pro
35 40 45

Asp Ser Phe Thr Thr Phe Leu Asp Leu Val Glu Arg Glu Leu Gly Pro
50 55 60

Leu Asp Ile Leu Val Asn Asn Ala
65 70

<210> 31

<211> 67

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 31

Ala Thr Asp Gly Ala Arg Val Ala Val Val Asp Leu His Ile Glu Ser
1 5 10 15

Ala Glu Glu Thr Val Ala Leu Ile Glu Ser Gln Tyr Gly Thr Pro Ala
20 25 30

Leu Ala Leu Glu Ala Asp Val Arg Asp Arg Ala Ala Val Ser Ala Ala
35 40 45

Phe Glu Ala Thr Val Ala Glu Trp Gly Arg Phe Asp Tyr Leu Val Asn
50 55 60

Asn Ala Gly
65

<210> 32

<211> 67

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 32

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Ala Ala Asp Gly Ala Arg Val Ala Val Val Asp Leu His Ile Glu Ser
1               5                   10                  15

Ala Lys Glu Thr Val Ala Leu Ile Glu Ser Gln Tyr Gly Thr Pro Ala
            20                  25                  30

Leu Ala Leu Glu Ala Asp Val Arg Asp Arg Ala Ala Val Ser Ala Ala
        35                  40                  45
Phe Glu Ala Thr Val Ala Glu Trp Gly Arg Phe Asp Tyr Leu Val Asn
    50                  55                  60

Asn Ala Gly
65
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<210> 33

<211> 348

<212> PRT

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 33

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Met Lys Ala Ile Gln Tyr Ala Arg Ile Gly Ala Glu Pro Glu Leu Thr
1               5                   10                  15

Glu Ile Pro Lys Pro Glu Pro Gly Pro Gly Glu Val Leu Leu Glu Val
            20                  25                  30

Thr Ala Ala Gly Val Cys His Ser Asp Asp Phe Ile Met Ser Leu Pro
        35                  40                  45

Glu Glu Gln Tyr Thr Tyr Gly Leu Pro Leu Thr Leu Gly His Glu Gly
    50                  55                  60

Ala Gly Arg Val Ala Ala Val Gly Glu Gly Val Glu Gly Leu Asp Ile
65                  70                  75                  80
```

```
Gly Thr Asn Val Val Val Tyr Gly Pro Trp Gly Cys Gly Ser Cys Trp
                85                  90                  95

His Cys Ser Gln Gly Leu Glu Asn Tyr Cys Ser Arg Ala Lys Glu Leu
            100                 105                 110

Gly Ile Asn Pro Pro Gly Leu Gly Ala Pro Gly Ala Leu Ala Glu Phe
        115                 120                 125

Met Ile Val Asp Ser Pro Arg His Leu Val Pro Ile Gly Asp Leu Asp
    130                 135                 140

Pro Val Lys Thr Val Pro Leu Thr Asp Ala Gly Leu Thr Pro Tyr His
145                 150                 155                 160

Ala Ile Lys Arg Ser Leu Pro Lys Leu Arg Gly Gly Ala Tyr Ala Val
                165                 170                 175

Val Ile Gly Thr Gly Gly Leu Gly His Val Ala Ile Gln Leu Leu Arg
            180                 185                 190

His Leu Ser Ala Ala Thr Val Ile Ala Leu Asp Val Ser Ala Asp Lys
        195                 200                 205

Leu Glu Leu Ala Thr Lys Val Gly Ala His Glu Val Val Leu Ser Asp
    210                 215                 220

Lys Asp Ala Ala Glu Asn Val Arg Arg Ile Thr Gly Ser Gln Gly Ala
225                 230                 235                 240

Ala Leu Val Leu Asp Phe Val Gly Tyr Gln Pro Thr Ile Asp Thr Ala
                245                 250                 255

Met Ala Val Ala Gly Val Gly Ser Asp Val Thr Ile Val Gly Ile Gly
            260                 265                 270

Asp Gly Gln Ala His Ala Lys Val Gly Phe Phe Gln Ser Pro Tyr Glu
        275                 280                 285

Ala Ser Val Thr Val Pro Tyr Trp Gly Ala Arg Asn Glu Leu Ile Glu
    290                 295                 300

Leu Ile Asp Leu Ala His Ala Gly Ile Phe Asp Ile Ala Val Glu Thr
305                 310                 315                 320
```

Phe Ser Leu Asp Asn Gly Ala Glu Ala Tyr Arg Arg Leu Ala Ala Gly
325 330 335

Thr Leu Ser Gly Arg Ala Val Val Val Pro Gly Leu
340 345

<210> 34

<211> 348

<212> PRT

<213> unknown
<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 34

Met Lys Ala Ile Gln Tyr Thr Arg Ile Gly Ala Glu Pro Glu Leu Thr
1 5 10 15

Glu Ile Pro Lys Pro Glu Pro Gly Pro Gly Glu Val Leu Leu Glu Val
20 25 30

Thr Ala Ala Gly Val Cys His Ser Asp Asp Phe Ile Met Ser Leu Pro
35 40 45

Glu Glu Gln Tyr Thr Tyr Gly Leu Pro Leu Thr Leu Gly His Glu Gly
50 55 60

Ala Gly Arg Val Ala Ala Val Gly Glu Gly Val Glu Gly Leu Asp Ile
65 70 75 80

Gly Thr Asn Val Val Val Tyr Gly Pro Trp Gly Cys Gly Ser Cys Trp
85 90 95

His Cys Ser Gln Gly Leu Glu Asn Tyr Cys Ser Arg Ala Lys Glu Leu
100 105 110

Gly Ile Asn Pro Pro Gly Leu Gly Ala Pro Gly Ala Leu Ala Glu Phe
115 120 125

Met Ile Val Asp Ser Pro Arg His Leu Val Pro Ile Gly Asp Leu Asp
130 135 140

Pro Val Lys Thr Val Pro Leu Thr Asp Ala Gly Leu Thr Pro Tyr His
145 150 155 160

Ala Ile Lys Arg Ser Leu Pro Lys Leu Arg Gly Gly Ala Tyr Ala Val
165 170 175

Val Ile Gly Thr Gly Gly Leu Gly His Val Ala Ile Gln Leu Leu Arg
180 185 190

His Leu Ser Ala Ala Thr Val Ile Ala Leu Asp Val Ser Ala Asp Lys
195 200 205

Leu Glu Leu Ala Thr Lys Val Gly Ala His Glu Val Val Leu Ser Asp
210 215 220

Lys Asp Ala Ala Glu Asn Val Arg Arg Ile Thr Gly Ser Gln Gly Ala
225 230 235 240

Ala Leu Val Leu Asp Phe Val Gly Tyr Gln Pro Thr Ile Asp Thr Ala
245 250 255

Met Ala Val Ala Gly Val Gly Ser Asp Val Thr Ile Val Gly Ile Gly
260 265 270

Asp Gly Gln Ala His Ala Lys Val Gly Phe Phe Gln Ser Pro Tyr Glu
275 280 285

Ala Ser Val Thr Val Pro Tyr Trp Gly Ala Arg Asn Glu Leu Ile Glu
290 295 300

Leu Ile Asp Leu Ala His Ala Gly Ile Phe Asp Ile Ala Val Glu Thr
305 310 315 320

Phe Ser Leu Asp Asn Gly Ala Glu Ala Tyr Arg Arg Leu Ala Ala Gly
325 330 335

Thr Leu Ser Gly Arg Ala Val Val Val Pro Gly Leu
340 345

<210> 35

<211> 488

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0050197= Pseudomonas oleovorans; ZF0050294= Rhodococcus; ZF0050330= Bacillus; ZF0051303= Bacterium; ZF0051337= Methylomonas; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002852= Rhodococcus; ZF0050310= Arthrobacter paraffineus; ZF0002862= Streptomyces clavuligerus; ZF0050292= Bacterium; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0002437= Streptomyces; ZF0003712= Micromonospora; ZF0003765= Streptomyces; ZF0051305= Bacterium; ZF0003513= Actinomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0002332= Streptomyces diastatochromogenes; ZF0003768= Actinomyces; ZF0002379= Streptomyces coelescens; ZF0002351= Nonomuraea roseoviolacea; ZF0003769= Actinomyces;

<400> 35
gggccatggg gttgtggcaa ctgttggcac tgctcacaag gactcgagaa ctattgctct
60

cgcgcccaag aactcggaat caatcctccc ggtctcggtg cacccggcgc gttggccgag
120

ttcatgatcg tcgattctcc tcgccacctt gtcccgatcg gtgacctcga cccggtcaag
180

acggtgccgc tgaccgacgc cggtctgacg ccgtatcacg cgatcaagcg ttctctgccg
240

aaacttcgcg gaggctcgta cgcggttgtc attggtaccg gcgggctcgg ccacgtcgcc
300

attcagctcc tccgtcacct ctcggcgtca acggtcatcg ctttggacgt gagcgcggac
360

aagctcgaac tggcaaccaa ggtaggcgct cacgaagtgg ttctgtccga caaggacgcg
420

gccgagaacg tccgcaagat cactggaagt caaggcgccg cactggttct cgacttcgtt
480

ggctacca
488

<210> 36

<211> 385

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0050197= Pseudomonas oleovorans; ZF0050294= Rhodococcus; ZF0050330= Bacillus; ZF0051303= Bacterium; ZF0051337= Methylomonas; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002852= Rhodococcus; ZF0050310= Arthrobacter paraffineus; ZF0002862= Streptomyces clavuligerus; ZF0050292= Bacterium; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0002437= Streptomyces; ZF0003712= Micromonospora; ZF0003765= Streptomyces; ZF0051305= Bacterium; ZF0003513= Actinomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0002332= Streptomyces diastatochromogenes; ZF0003768= Actinomyces; ZF0002379= Streptomyces coelescens; ZF0002351= Nonomuraea roseoviolacea; ZF0003769= Actinomyces;
<400> 36
gggccatggg gttgtggcaa ctgttggcac tgctcacaag gactcgagaa ctattgctct
60

cgcgcccaag aactcggaat caatcctccc ggtctcggtg cacccggcgc gttggccgag
120

ttcatgatcg tcgattctcc tcgccacctt gtcccgatcg gtgacctcga cccggtcaag
180

acggtgccgc tgaccgacgc cggtctgacg ccgtatcacg cgatcaagcg ttctctgccg
240

aaacttcgcg gaggctcgta cgcggttgtc attggtaccg gcgggctcgg ccacgtcacc
300

attcagctcc tccgtcacct ctcggcggca acggtcatcg ctttggacgt gagcgcggac
360

aagctcgaac tggcaaccaa ggtag
385

<210> 37

<211> 486

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050286= Corynebacterium hoagii

<400> 37
ggcccttggg gttgcggacg ttgctggcac tgcgcgcagg ggctcgagaa ctactgctcc 60

cgcgcaaggg aactcggcat cgccccaccc ggcttgggcg cgccgggcgc gatcgccgag 120

tacatgatcg tcgactcgcc gcgtcacctg gtcccgatcg gtgacctcga ccccgtcacg 180

acggtgccgc tgaccgacgc cgggctcacc ccgtaccacg cgatcaaacg gtcgctcggc 240

aagctccgcg ccggctcgta cgcagtcgtg atcggcaccg gaggcctcgg acacgtcggc 300

atccagctgc tccgccacct gtcccctgca cgcatcatcg ccctcgacgt caacgacgag 360

aagctcgcgt tcgcccgcga ggtcggcgcg cacgagaccg tgttgtcgaa cgccgacgcc 420

gccgcgaacg tccggaagat cacgggttcg gccggtgccg cgctggtcct agacttcgtc 480

ggctac 486

<210> 38

<211> 483

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 38
ggcccatggg gctgtggcag ctgttggcac tgctcgcaag gactcgaaaa ctactgttct 60

cgggcaaaág aactcggcat caatcctcct ggtctcggtg cacccggcgc gttggccgaa 120

ttcatgatcg tcgattcacc tcgccacctc gtcccgatcg gcgacctcga tccggtcaag 180

acggtgccac tgaccgacgc cggtctgact ccgtatcacg cgatcaagcg ttcactgccg 240

aaacttcgcg gtggcgcgta cgccgtcgtc atcggtaccg gcggtctcgg ccatgtcgcc 300

atccaactcc tccgccacct ctcggcagca accgtcatcg cactcgacgt gagcgcggac
360

aagctcgtac tggcaaccaa ggtaggcgct cacgaagtgg tcctgtccga caaggacgcg
420

gccgagaacg tccgcaggat caccggaagt cagggcgccg cactggttct tgacttcgtt
480

ggc
483

<210> 39

<211> 210

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0004210= Actinomyces; ZF0004212= Actinomyces; ZF0004211= Actinomyces; ZF0003860= Actinomyces; ZF0004218= Actinomyces; ZF0003868= Actinomadura; ZF0004213= Actinomyces; ZF0003876= Actinomyces; ZF0003866= Actinomyces; ZF0003864= Actinomyces; ZF0003862= Actinomadura; ZF0003869= Actinomyces; ZF0003867= Actinomadura; ZF0004216= Actinomyces; ZF0004235= Actinomyces; ZF0004209= Actinomadura; ZF0004214= Actinomyces; ZF0003871= Actinomyces; ZF0004063= Actinomadura; ZF0004052= Actinomadura; ZF0006405= Streptomyces; ZF0003865= Actinomadura; ZF0004047= Actinomadura; ZF0004070= Actinomyces; ZF0004085= Actinomyces; ZF0004217= Actinomyces; ZF0004089= Actinomadura; ZF0004090= Actinomadura; ZF0006138= Streptomyces; ZF0004236= Actinomadura; ZF0051203= Bacterium;

<400> 39
ggaccgtggg gctgcggcac gtgcgtcaag tgcgccgagg gcaaggagaa ctactgcctg
60

cgcgccaagg aactcggcat cgccccgccc ggactcggct cgcccggcgc catggccgag
120

tacatgatcg tcgacgaccc gcgccacctg gtgccgctcg gcggtctcga cccggtccag
180

gccgtgccgc tcactgacgc gggcctgaca
210

<210> 40

<211> 282

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821= Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 40
tgtcacaccg atcaccacat cgtcaccggc gcgaccccga tgccgtcgtt cccggtcatg
60

ggcgggcacg agggttcggg cgtcatcacc aagctcggcc ctgaggtcaa gggactggag
120

gtcggcgacc acgtcgttct gtccttcatt ccggcttgtg gaacctgtcc ggcgtgttcg
180

gccgggcatc agaatctttg tgacctcggg atgggcctcc tcagcggcca agccatcagc
240

gacggcacgt accggatcca ggctcgcggc gaaaacgtga tc
282

<210> 41

<211> 276

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821=

Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 41
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ggccacgaag gcgcgggcat agtggagaaa gtcggccccg gcgtgcgaga cgtcgaggta 120

ggcgatcacg tcgtcctctc cttcattccc tcgtgtggac gctgccgttg gtgcgcagtc 180

ggacagagca acctctgcga cctcggcgcc attctgatgg ccggcgcaca ggtcgacggg 240

acgtaccgcg cgacagctcg cgggcacgac gtcgga 276

<210> 42

<211> 276

<212> DNA

<213> unknown

<220>

<221> source

<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821= Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 42
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ggccacgaag gcgcgggcat agtggagaaa gtcggccccg gcgtgcgaga cgtcgaggta 120

ggcgatcacg tcgtcctctc cttcattccc tcgtgtggac gctgccgttg gtgcgcagtc 180

ggacagagca acctctgcga cctcggcgcc attctgatgg ccggcgcaca ggtcgacggg
240

acgtaccgcg cgacagctcg cgggcacgac gtcgga
276

<210> 43

<211> 276

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821= Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 43
tgtcatactg acgatcatgc tgtgaccggt gatctggcag tcccactccc cgtgatcggt
60

ggccacgaag gcgcgggcat agtggagaaa gtcggccccg gcgtgcgaga cgtcgaggta
120

ggcgatcacg tcgtcctctc cttcattccc tcgtgtggac gctgccgttg gtgcgcagtc
180

ggacagagca acctctgcga cctcggcgcc attctgatgg ccggcgcaca ggtcgacggg
240

acgtaccgcg cgacagctcg cgggcacgac gtcgga
276

<210> 44

<211> 276

<212> DNA

<213> unknown

<220>

<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821= Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 44
tgtcacaccg acgatcatgc tgtgaccggt gatctggcag tcccactccc cgtgatcggt
60

ggccacgaag gcgcgggcat agtggagaaa gtcggccccg gcgtgcgaga cgtcgaggta
120

ggcgatcacg tcgtcctctc cttcattccc tcgtgtggac gctgccgttg gtgcgcagtc
180

ggacagagca acctctgcga cctcggcgcc attctgatgg ccggcgcacg ggtcgacggg
240

acgtaccgcg cgacagctcg cgggcacgac gtcgga
276

<210> 45

<211> 276

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002326= Actinoplanes missouriensis; ZF0003505= Streptomyces; ZF0051321= Bacterium; ZF0050782= Lactobacillus bulgaricus; ZF0050544= Phyllobacterium rubiacearum; ZF0002031= Streptomyces; ZF0002349= Streptomyces spectabilis; ZF0002434= Streptomyces; ZF0050993= Kocuria; ZF0002018= Streptomyces; ZF0003767= Actinomyces; ZF0003764= Streptomyces; ZF0002331= Actinoplanes philippinensis; ZF0002441= Streptomyces; ZF0051307= Bacterium; ZF0051301= Bacterium; ZF0051240= Bacterium; ZF0002333= Rhodococcus erythropolis; ZF0003713= Micromonospora; ZF0004980= Streptomyces; ZF0004821=

Actinomyces; ZF0002359= Actinoplanes ianthinogenes; ZF0002396= Actinoplanes; ZF0003781= Actinomyces; ZF0003512= Actinomyces; ZF0006093= Streptomyces; ZF0006103= Streptomyces; ZF0006087= Streptomyces; ZF0050446= Bacterium; ZF0050445= Bacterium; ZF0006086= Streptomyces; ZF0002322= Rhodococcus; ZF0003538= Actinomyces; ZF0003535= Actinomyces;

<400> 45
tgtcacactg acgatcatgc tgtgaccggt gatctggcag tcccactccc cgtgatcggt
60

ggccacgaag gcgcgggcat agtggagaaa gtcggccccg gcgtgcgaga cgtcgaggta
120

ggcgatcacg tcgtcctctc cttcattccc tcgtgtggac gctgccgttg gtgcgcagtc
180

ggacagagca acctctgcga cctcggcgcc attctgatgg ccggcgcaca ggtcgacggg
240

acgtaccgcg cgacagctcg cgggcacgac gtcgga
276
<210> 46

<211> 279

<212> .DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 46
tgccacacag atctgttcac gaagtcggtg ctaccggaaa ggctcggccc ctgcgtgttc
60

gggcacgaag gagcgggggt ggtcgaggcc gtcggctcgt cgatcgacag cattgcgccc
120

ggtgatcacg tgttgctgag ctaccgcagt tgcggtgtgt gcaggcagtg cctcagcggt
180

catcgggcgt actgcgaaag ctcacacggg ctcaacagct ctggcgcacg caccgacggc
240

tcgacgccgg tccggcgaag cggaactccg atacggtcc
279

<210> 47

<211> 279

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002333= Rhodococcus erythropolis

<400> 47
tgtcatactg atctgttcac gaagacggtg ctaccggaaa agctcgggcc ctgcgtgttc
60

ggacacgaag gcgccggcgt cgtgcaagcc gttggctcgt cgatcgacaa catcgcggct
120

ggtgatcacg tattgctgag ctaccgcagt tgcggtgtat gcaggcaatg tctcagcgac
180

catcgggcgt actgcgaaag ctcacacggg ctcaacagct ctggcgcacg caccgacggc
240

tcgacgccgg tccggcgaaa cggaactccg atacggtcc
279

<210> 48

<211> 360

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0051303= Bacterium; ZF0051337= Methylomonas; ZF0002862= Streptomyces clavuligerus; ZF0050292= Bacterium; ZF0051305= Bacterium; ZF0003513= Actinomyces; ZF0002351= Nonomuraea roseoviolacea; ZF0003769= Actinomyces; ZF0002017= Streptomyces; ZF0051306= Bacterium; ZF0002016= Streptomyces; ZF0003504= Actinomyces; ZF0006073= Streptomyces; ZF0003770= Actinomyces; ZF0002352= Actinoplanes italicus; ZF0002378= Streptomyces aureomonopodiales; ZF0006089= Streptomyces; ZF0006106= Streptomyces; ZF0051325= Bacterium; ZF0006108= Streptomyces; ZF0002440= Streptomyces; ZF0051302= Bacterium; ZF0003532= Actinomyces; ZF0003548= Nocardiaform;

<400> 48
tgcgggacgg accgcgagat cgcctcgggc atctacgggt gggcgccgcc gggacgcgaa
60

cacctcgtcc tcgggcacga atcgctgggc cgagtacgca ccgcgcccga cggcagcggt
120

ttcgccgccg gtgatctcgt cgtcgggatc gtgcgcaggc ccgatccggt gccgtgcggg
180

gcgtgtgcgc acggtgagtt cgacatgtgc cgcaacggtg agtacgtcga gcgcgggatc
240

aagcagatcg acgggtacgg gtcgacgtcg tgggtggtgg acgccgacta cacggtcaag
300

ctggacccgg cgctcaccga ggtgggtgtg ctgatggaac cgacgacggt gcttggccaa
360

<210> 49

<211> 421

<212> DNA

<213> unknown

<220>

<221> source
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<400> 49
tgtggtaccg acctgcacat ccggtcctgg gacggatggg cgcagaagac catcgccacc
60

ccgctcacgc tcggccacga gttcgtcggc gaggtcgtcg agaccggccg cgacgtgacc
120

gacatccagg tcggcgacct ggtcagcggc gagggccacc tggtctgcgg caagtgccgc
180

aactgcctgg ccggccgccg tcacctgtgc cgcgcgaccg tcggcctcgg tgtcggccgt
240

gacggcgcct tcgccgagta cgtggtgctg cccgcctcca acgtgtgggt gcaccgggtg
300

ccggtcgacc tcgacgtcgc cgcgatcttc gacccgttcg gcaacgcggt gcacaccgcg
360

ctctccttcc cgctcgtcgg cgaggacgtg ctggtcaccg gtgccggtac catcggcatc
420

t
421

<210> 50

<211> 414

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050197= Pseudomonas oleovorans; ZF0050294= Rhodococcus; ZF0050330= Bacillus, ZF0002852= Rhodococcus; ZF0050310= Arthrobacter paraffineus; ZF0002437= Streptomyces; ZF0003712= Micromonospora; ZF0003765= Streptomyces; ZF0002332= Streptomyces diatsatochromogenes; ZF0003768= Actinomyces; ZF0002379= Streptomyces coelescens; ZF0002443= Streptomyces; ZF0002442= Streptomyces; ZF0002436= Streptomyces; ZF0050994= Bacterium; ZF0050992= Bacterium; ZF0050442= Bacterium; ZF0002049= Streptomyces; ZF0006069= Streptomyces; ZF0006075= Streptomyces; ZF0004724= Nocardiaform; ZF0002392= Actinoplanes nipponensis; ZF0002356= Actinoplanes brasiliensis; ZF0003501= Actinomyces; ZF0051322= Bacterium; ZF0006078= Streptomyces; ZF0006092= Streptomyces; ZF0006090= Streptomyces; ZF0006084= Streptomyces; ZF0006068= Streptomyces; ZF0050284= Rhodococcus; ZF0050028= Agrobacterium tumefaciens; ZF0003540= Actinomyces; ZF0003528= Actinomyces; ZF0003529= Actinomyces;

<400> 50
ggcctgacga tcggccatga accggtgggc gtcatcgaaa agctgggcag cgccgtgacg
60

ggttaccgcg agggccaacg cgtgatcgcc ggcgcgatct gccccaactt caattcgtat
120

gccgcgcagg atggcgcgcc gtcgcaggat ggcagctacc tggtggccag cggcgcatgc
180

ggctgccatg gataccgggc cacggccggc tggcgctttg gcaacatcat cgatggcgcc
240

caggccgaat acctgctggt tcccgatgcg cagggcaatc tggcgccggt tccggacaac
300

ctgagcgatg aacaggtgct gatgtgcccg gacatcatgt ccaccggctt caaaggcgca
360

gagaacgcac acatccgcat cggcgacacg gtggcggtat ttgcgcaggg acca
414

<210> 51

<211> 432

<212> DNA

<213> unknown

<220>

<221> source

<223> ZF0050197= Pseudomonas oleovorans; ZF0050294= Rhodococcus; ZF0050330= Bacillus, ZF0002852= Rhodococcus; ZF0050310= Arthrobacter paraffineus; ZF0002437= Streptomyces; ZF0003712= Micromonospora; ZF0003765= Streptomyces; ZF0002332= Streptomyces diatsatochromogenes; ZF0003768= Actinomyces; ZF0002379= Streptomyces coelescens; ZF0002443= Streptomyces; ZF0002442= Streptomyces; ZF0002436= Streptomyces; ZF0050994= Bacterium; ZF0050992= Bacterium; ZF0050442= Bacterium; ZF0002049= Streptomyces; ZF0006069= Streptomyces; ZF0006075= Streptomyces; ZF0004724= Nocardiaform; ZF0002392= Actinoplanes nipponensis; ZF0002356= Actinoplanes brasiliensis; ZF0003501= Actinomyces; ZF0051322= Bacterium; ZF0006078= Streptomyces; ZF0006092= Streptomyces; ZF0006090= Streptomyces; ZF0006084= Streptomyces; ZF0006068= Streptomyces; ZF0050284= Rhodococcus; ZF0050028= Agrobacterium tumefaciens; ZF0003540= Actinomyces; ZF0003528= Actinomyces; ZF0003529= Actinomyces;

<400> 51
tgcgggacgg acctgcacat cctcggaggt gacgtccccg aggtgaccga cgggcgaatc
60

ctgggccacg aggccgtcgg gaccgtggtc gaggtgggcg acggcgtaca gacactcgcg
120

ccgggcgatc gcgtgctcgt ctcgtgtgtc accgcatgcg gtacgtgccg gttctgccgc
180

gagagccgct acgggcaatg cctcggaggc ggcggctgga tcctcggaca cctgatcgac
240

ggcacccagg ccgaactcgt ccgagttccg tacgccgaca attcgaccca ccgcatcccc
300

gacggtgtga gcgacgagca gatgctcatg ctcgccgaca tcctgcccac ctcctacgag
360

gtcggtgttc tcaacggctg tctccggccg gcggacgtcg tcgtcatcat cggggccgac
420

gatcggcctc tt
432

<210> 52

<211> 220

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 52
cgtcgacgtc gtcgtcgaca acgcgggatt cggaacacac ggggcattcg tggacgaaga
60

tcacgagcgc gtcacgtccg agattcagct caacatcgcc acgctggtcg agctgacaca
120

cacattcccg cccgaccttc tcaccggccg cggagcactg gtcaacatcg ccagcacagc
180

gtcgttccag ccgacaccgg gcatggccgt ctactgcgct
220

<210> 53

<211> 226

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 53
cgtcgacgtc gtcgtccaca acgccggatt cggaacacac ggggcattcg tggacgaaga
60

tctcgagcgc gtcacgtccg agattcagct caacatcgcc acgctggtcg agctgacaca
120

cacattcctg cccgaccttc tcaccggccg cggagcactg gtcaacatcg ccagcacagc
180

gtcgttccag ccgacaccgg gcatggccgt ctactgcgcc accaag
226

<210> 54

<211> 237

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0003535= Actinomyces

<400> 54
cgtgtcgacg tcgtggtgca caatgctgcg atcactcaaa aggccacttt tcgcgacatt
60

acccccgccg attttgagcg catcctgcgg gtgaacctga ccggcgtctt caacctgagc
120

caagccgtca ttcccttgat gattcagcgc ggcggaggaa gcatcgtctc gatttcctcg 180

ctgtcggcgc agaacggcgg ggggatcttc ggcggcgccc actattgcgc aaccaag 237

<210> 55

<211> 229

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0003535= Actinomyces

<400> 55
cgtcgacgtc gtcgtcgaca acgccggtct ggcactgggc acggcccccg cgccgcaggt 60

gccgctaaag gactggcaga ccatggtgaa caccaacatc accggtctac tgaacatcac 120

ccaccatctc ctgccgacac tgatcgaccg taaaggtatc gtcgtcaacc tttcgtctgt 180

tgccgcgcac tatccctata cgggcggcaa tgtatactgc gcctccaag 229

<210> 56

<211> 216

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 56
caggggatcg gatacgccac cgcgaagcgg ctgatcagcc tgggtgcgac ggtcgcgatc 60

ggcgacatcg acgaagccac tctcgcgcga gcagccaagg atttgggcat ccgcacgttc 120

gggcgcctcg acgtcaccga ccccgcctcg ttcttcgact tcctcgacac cgtcgaaggt 180

gaactcggcc cgatcgacgt gctgatcaac aacgcg 216

<210> 57

<211> 225

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0080310= Arthrobacter paraffineus

<400> 57
cagcggatcg ggctcgaaat tgcgcgcacc ttcatcaagg aaggcgcgac cgtcgttctc
60

ggcgacatca acgaaaccgt gggaacggct gcggtcgccg aactcggtgg agagtcggtc
120
gcccgtttcg cttcctgcga cgtgcgtgac tccggacagg tcgaggccat gctcgatctg
180

gccgaaagcg ctttcggtcc agtcgatgtc atgatgaaca acgcg
225

<210> 58

<211> 216

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0080310= Arthrobacter paraffineus

<400> 58
caggggatcg gctaccagac cgcgaaggag ctgatccgac gaggtcaccg cgtggccatc
60

ggcgacatcg acgaggcacg tgctaaggag accgccgccg aactgggggt taaggttgtc
120

acccgcctcg atgtcaccga ccctgactcg ttcaaagact ttctcgacct agtcgaggga
180

gacctcggcc ccctcgacgt gctgatcaac aacgcg
216

<210> 59

<211> 222

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0080310= Arthrobacter paraffineus

<400> 59
gggatcgggc tcgaaattgc gcgcaccttc atcaaggaag gcgcgaccgt cgttctcggc 60

gacatcaacg aaaccgtggg aacggctgcg gtcgccgaac tcggtggaga gtcggtcgcc 120

cgtttcgctt cctgcgacgt gcgtgactcc ggacaggtcg aggccatgct cgatctggcc 180

gaaagcgctt tcggtccagt cgatgtcatc gtgaacaacg cg 222
<210> 60

<211> 222

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0080310= Arthrobacter paraffineus

<400> 60
atcgggctcg aaattgcgcg caccttcatc aaggaaggcg cgaccgtcgt tctcggcgac 60

atcaacgaaa ccgtgggaac ggctgcggtc ggcgaactcg gtggagagtc ggtcgcccgt 120

ttcgcttcct gcgacgtgcg tgactccgga caggtcgagg ccatgctcga tctggccgaa 180

agcgctttcg gtccagtcga tgtcatggtc aacaacgccg gc 222

<210> 61

<211> 186

<212> DNA

<213> unknown

<220>

<221> source

<223> ZF0002333= Rhodococcus erythropolis

<400> 61
gtgccggtcg cggtcgtgga ccttcacatc gaaagtgcaa aggagaccgt cgcacttatc
60

gaatcgcagt acggcacacc cgcgctcgcc cttgaggccg atgtgcgcga ccgcgccgcc
120

gtgagcgccg ctttcgaagc caccgtcgcc gaatggggac gcttcgacta cctcgtcaac
180

aacgcc
186

<210> 62

<211> 222

<212> DNA
<213> unknown

<220>

<221> source
<223> ZF0002333= Rhodococcus erythropolis

<400> 62
ctcggccgtg aaatcgctct caagctcgct tccgaaggcg cctcggtagt ggtcaacgac
60

ctcgatcccg aacctgccgc tcagaccgag cgcgatatca aagccacagg tggacaggct
120

gtctcgtgcg tcggctccgt tgccgaggac gggttcgccg aacgcttcgt gaacactgcc
180

gtcgaatcat tcggcggact cgacgtcatg gtgaacaacg cg
222

<210> 63

<211> 231

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0002333= Rhodococcus erythropolis

<400> 63
gcggggctcg gagtggaatt cgctcaccgc ttcgccgctc gcggtgcaaa tctggttctc
60

gtcgccaggc gggcagatcg cctcgaagcc ctcgctaccg aactccgcgt cgcccacggc
120

atcacagtca cagttctgcc tgccgacctg gcggcgcccg gcgtcggcgc aacactgcac
180

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231

<210> 64

<211> 216

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0003535= Actinomyces

<400> 64
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60

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120

acccgactcg acgtcaccga acctgactcg ttcacaacgt ttctggacct ggtcgaacgt
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gaactcggac ccctcgacat cctggtcaac aacgcg
216

<210> 65

<211> 201

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

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gccacggacg gtgcccgcgt cgcggtcgtg gaccttcaca tcgaaagtgc agaggagacc
60

gtcgcactta tcgaatcgca gtacggcaca cccgcgctcg cccttgaggc cgatgtgcgc
120

gaccgcgccg ccgtgagcgc cgctttcgaa gccaccgtcg ccgaatgggg acgcttcgac
180

tacctcgtca acaacgccgg c
201

<210> 66
<211> 201

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

<400> 66
gccgcggacg gtgcccgcgt cgcggtcgtg gaccttcaca tcgaaagtgc aaaggagacc
60

gtcgcactta tcgaatcgca gtacggcaca cccgcgctcg cccttgaggc cgatgtgcgc
120

gaccgcgccg ccgtgagcgc cgctttcgaa gccaccgtcg ccgaatgggg acgcttcgac
180

tacctcgtca acaacgccgg c
201

<210> 67

<211> 1047

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

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cccgagcccg gtccaggtga agtgctcctg gaagtcaccg ctgccggcgt ctgccactcg
120

gacgacttca tcatgagcct gcccgaagag cagtacacct acggccttcc tctcacgctc
180

ggccacgaag gcgccggccg ggtcgccgcc gtcggcgagg gcgtcgaagg actcgacatc
240

ggaaccaatg tcgtcgtcta cggaccctgg ggctgtggca gctgttggca ctgctcgcaa
300

ggactcgaaa actactgttc tcgggcaaaa gaactcggca tcaatcctcc tggtctcggt 360

gcacccggcg cgttggccga attcatgatc gtcgattcac ctcgccacct cgtcccgatc 420

ggcgacctcg atccggtcaa gacggtgcca ctgaccgacg ccggtctgac tccgtatcac 480

gcgatcaagc gttcactgcc gaaacttcgc ggtggcgcgt acgccgtcgt catcggtacc 540

ggcggtctcg gccatgtcgc catccaactc ctccgccacc tctcggcagc aaccgtcatc 600

gcactcgacg tgagcgcgga caagctcgaa ctggcaacca aggtaggcgc tcacgaagtg 660

gtcctgtccg acaaggacgc ggccgagaac gtccgcagga tcaccggaag tcagggcgcc 720
gcactggttc tcgacttcgt cggctatcag cccaccatcg acaccgcgat ggctgtcgcc 780

ggcgtcggat cggacgtcac gatcgtcggg atcggcgacg ggcaggccca tgccaaagtc 840

gggttcttcc aaagtcctta cgaggcttct gtgacagttc cgtactgggg tgcccgcaac 900

gagctgatcg aattgatcga cctggcgcac gccggcatct tcgacatcgc ggtggagacc 960

ttcagtctcg acaacggcgc cgaagcgtat cgacgactgg ccgccggaac gctcagcggc 1020

cgcgcggttg tggtccctgg tctgtag 1047

<210> 68

<211> 1047

<212> DNA

<213> unknown

<220>

<221> source
<223> ZF0050310= Arthrobacter paraffineus

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gacgacttca tcatgagcct gccccgaagag cagtacacct acggccttcc tctcacgctc
180

ggccacgaag gcgccggccg ggtcgccgcc gtcggcgagg gcgtcgaagg actcgacatc
240

ggaaccaatg tcgtcgtcta cggaccctgg ggctgtggca gctgttggca ctgctcgcaa
300

ggactcgaaa actactgttc tcgggcaaaa gaactcggca tcaatcctcc tggtctcggt
360

gcacccggcg cgttggccga attcatgatc gtcgattcac ctcgccacct cgtcccgatc
420

ggcgacctcg atccggtcaa gacggtgcca ctgaccgacg ccggtctgac tccgtatcac
480

gcgatcaagc gttcactgcc gaaacttcgc ggtggcgcgt acgccgtcgt catcggtacc
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600

gcactcgacg tgagcgcgga caagctcgaa ctggcaacca aggtaggcgc tcacgaagtg
660

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720

gcactggttc tcgacttcgt cggctatcag cccaccatcg acaccgcgat ggctgtcgcc
780

ggcgtcggat cggacgtcac gatcgtcggg atcggcgacg ggcaggccca tgccaaagtc
840

gggttcttcc aaagtcctta cgaggcttct gtgacagttc cgtactgggg tgcccgcaac
900

gagctgatcg aattgatcga cctggcgcac gccggcatct tcgacatcgc ggtggagacc
960

ttcagtctcg acaacggcgc cgaagcgtat cgacgactgg ccgccggaac gctcagcggc
1020

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